BLA Clinical Review Memorandum

Application Type	Supplemental BLA
STN	125614/398
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Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Darcie Everett, MD, MPH Paula Ehrlich Agger, MD, MPH
Review Completion Date / Stamped Date	July 23, 2021
Supervisory Concurrence	Andrea Hulse, MD
Applicant	GlaxoSmithKline Biologicals SA, d/b/a GlaxoSmithKline
Established Name	Zoster Vaccine Recombinant, Adjuvanted
(Proposed) Trade Name	Shingrix
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Recombinant glycoprotein E subunit vaccine with $AS01_B$ adjuvant (QS21 and MPL with liposomes)
Dosage Form(s) and Route(s) of Administration	Lyophilized glycoprotein E antigen with liquid $AS01_B$ adjuvant in separate monodose vials, reconstituted prior to administration
Dosing Regimen	Two intramuscular administrations two to six months apart or, for individuals who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule, two intramuscular administrations one to two months apart.
Indication(s) and Intended Population(s)	The prevention of herpes zoster (HZ) (shingles) in adults aged 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy.
Orphan Designated (Yes/No)	No

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GLOSSARY

Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AIHA	autoimmune hemolytic anemia
AML	acute myeloid leukemia
ART	antiretroviral therapy
$AS01_B$	adjuvant at full concentration
$AS01_E$	adjuvant at half concentration
ATP	according to protocol
autoHCT	autologous hematopoietic stem cell transplant
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIS	calcineurin inhibitors or sirolimus
CLL	chronic lymphocytic leukemia
CMC	chemistry, manufacturing, and controls
CMI	cell-mediated immunogenicity
CoP	correlate of protection
cPRA	calculated panel reactive antibody
CRP	C-reactive protein
CS	corticosteroids
CSR	clinical study report
D	day
DART	developmental and reproductive toxicity
DVRPA	Division of Vaccines and Related Products Applications
DVT	deep vein thrombosis
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOP2	end of phase 2
GBS	Guillain-Barré syndrome
GCP	good clinical practice
GD	gestation day
gE	glycoprotein E
GI	gastrointestinal
GMC	geometric mean concentration
GMR	geometric mean ratio
GSK	GlaxoSmithKline
HCT	hematopoietic stem cell transplant
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HLA	human leukocyte antigen
HLGT	higher level group term
HLT	higher level term
HZ	herpes zoster
HZAC	Herpes Zoster Adjudication Committee
HZ/su	herpes zoster subunit vaccine (Trade name Shingrix)
IC	immunocompromised

IFN	interferon
IND	investigational new drug
ILD	interstitial lung disease
IL	interleukin
ILI	influenza-like illness
IM	intramuscular
iPSP	initial pediatric study plan
IR	information request
IS	injection site
ISS	integrated summary of safety
ITP	immune thrombocytopenic purpura
LB	lower bound
LD	lactation day
LMP	last menstrual period
M	month
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MC	mycophenolate compounds
MGI	mean geometric increase
MHC	major histocompatibility complex
MM	multiple myeloma
MPL	monophosphoryl lipid A
MRI	magnetic resonance imaging
mTVC	modified total vaccinated cohort
NHBCL	non-Hodgkin B cell lymphoma
NHTCL	non-Hodgkin T cell lymphoma
ON	optic neuritis
OVRR	Office of Vaccines Research and Review
PAT	prophylactic antiviral therapy
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PeRC	Pediatric Review Committee
PHN	post-herpetic neuralgia
PI	prescribing information
pIMD	potential immune-mediated disease
PMC	postmarketing commitment
PRA	panel reactive Ab
PREA	Pediatric Research Equity Act
PT	Preferred Term
PVP	pharmacovigilance plan
PY	person-years
SAE	serious adverse event
sBLA	supplemental Biologics License Application
SD	standard deviation
SDTM	Study Data Tabulation Model
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TNF	tumor necrosis factor
TVC	total vaccinated cohort
US	United States
VE	vaccine efficacy

VRR	vaccine response rate
VZV	varicella zoster virus
YOA	years of age
YO	year-old
ZBPI	Zoster Brief Pain Inventory

1. EXECUTIVE SUMMARY

The Applicant, GlaxoSmithKline (GSK), has submitted an efficacy supplement to their Biologics License Application (sBLA 125614/398) for Shingrix (Zoster Vaccine Recombinant, Adjuvanted) to: 1) expand the population for use to include individuals 18 through 49 years of age who are or will be at increased risk of herpes zoster (HZ) due to immunodeficiency or immunosuppression caused by known disease or therapy, and 2) include a new dosing schedule with an interval of 1 to 2 months between the first and second dose for the immunocompromised (IC) population. Shingrix, a recombinant glycoprotein E (gE) subunit vaccine with $AS01_B$ adjuvant (hereafter referred to as HZ/su), was originally approved for use on October 20, 2017, for adults ≥50 YOA for the prevention of HZ, with a dosing regimen of two doses administered 2 to 6 months apart. With approval of this sBLA, the Indications and Usage section of the Prescribing Information is being revised to include use "in adults 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy." The Dosage and Administration section of the Prescribing Information is being revised to include a dosing interval of 1 to 2 months between doses for individuals who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule.

HZ is a condition caused by reactivation of the latent varicella zoster virus (VZV) following primary VZV infection, usually as varicella (chickenpox), in childhood. HZ occurs due to a decline in cell-mediated immunogenicity associated with advancing age or immunocompromise, and generally presents as a unilateral, vesicular rash in a single dermatome accompanied by pain, which may be severe and persistent. Approximately one million cases of HZ occur annually in the United States (US), and it is estimated that one in three people experience HZ in their lifetime. HZ incidence in IC individuals has been estimated to be approximately twice that of immunocompetent individuals (Schröder et al. 2017; Muñoz-Quiles et al. 2020), with individuals who undergo hematopoietic stem cell transplants (HCTs) having the highest known incidence of HZ (40 – 60/1000 person-years [PY]) (Sahoo et al. 2017; Schröder et al. 2017; Mao et al. 2018). The incidence of severe HZ and HZ complications is higher in IC individuals as compared to immunocompetent individuals.

In support of expanding the use of the vaccine to include individuals 18 through 49 YOA at increased risk of HZ due to immunodeficiency or immunocompromise, the Applicant submitted the results of six randomized, observer-blind, placebo-controlled trials in five IC populations, representing 1,587 IC subjects who received at least one dose of HZ/su. In each of these studies, HZ/su was administered intramuscularly with a one- to two-month interval between the first and second dose. Efficacy of a two-dose series in the prevention of HZ was evaluated based on a clinical disease endpoint in Zoster-002 in subjects who had recently received an autologous HCT (autoHCT) and as a post hoc analysis in Zoster-039 in subjects with hematologic malignancies. The other trials evaluated the safety and immunogenicity of HZ/su and along with the results of Zoster-002 and Zoster-039 were viewed by CBER as supportive of effectiveness and the favorable risk benefit profile in these IC populations.

In Zoster-002 and Zoster-039, clinically suspected HZ cases were documented by rash history, digital photography, and sampling of available rash lesions for polymerase chain reaction (PCR) assay to test for VZV. Additional visits were scheduled for clinically suspected HZ cases at which time information relevant to the suspected HZ episode was recorded, such as concomitant medications, medical attention, or HZ-related complications. Subjects with clinically suspected HZ completed Zoster Brief Pain Inventory (ZBPI) and quality of life questionnaires to

document HZ-associated pain and assess health-related quality of life. Duration of HZ-associated pain was based on a subject reporting a 28-day/4-week pain-free interval. Cases of HZ were confirmed in a hierarchical manner; while all cases were adjudicated by an expert Herpes Zoster Adjudication Committee (HZAC), the HZAC ruling served as final case confirmation only if a case could not be confirmed or excluded by PCR testing of lesion samples. The analysis of prophylactic vaccine efficacy, the pre-specified primary endpoint for Zoster-002 and a post hoc analysis for Zoster-039, was performed in the modified total vaccinated cohort (mTVC), which consisted of subjects who received two doses and did not report a confirmed case of HZ prior to one month after dose 2. In Zoster-002, confirmed cases occurring after treatment for disease relapse were not included in the analysis. In some of the other supportive studies (e.g., Zoster-015, Zoster-028 and Zoster-041) suspected cases of HZ were recorded but not confirmed.

In each of the trials, collection of safety data was similar and included solicited local (injection site pain, swelling and redness) and general (fever, headache, myalgia, gastrointestinal (GI) symptoms, shivering and fatigue) signs and symptoms recorded on a diary card by all subjects for seven days (Days 0 – 6) following each vaccination, unsolicited adverse events (AEs), including those that were medically attended, recorded on a diary card for 30 days post-vaccination, serious adverse events (SAEs) and potential immune-mediated diseases (pIMDs) collected for at least one year post-vaccination. Safety outcomes pertinent to the underlying disease of the particular IC population were also collected during each trial.

Zoster-002: this study was a Phase 3, observer-blind, randomized, placebo-controlled trial designed to assess the efficacy, safety, and immunogenicity of HZ/su. Zoster-002 constitutes the largest trial in this submission, enrolling 1,846 adults who received an autoHCT 50 – 70 days prior to vaccination. Prophylactic antiviral therapy (PAT) with activity against HZ was allowed; subjects with planned PAT for more than six months were excluded. Individuals with varicella or HZ, or vaccination against varicella or HZ, within the previous 12 months were excluded. The conditions for the analyses of the primary efficacy endpoint were in part event driven, based on the number of confirmed HZ cases as well as a minimum follow-up period of 12 months following the last vaccination for all subjects to ensure adequate safety and efficacy data collection. Secondary objectives included evaluation of HZ/su vaccine efficacy (VE) in the prevention of post-herpetic neuralgia (PHN) and HZ-related complications (evaluated in all subjects, not only in subjects with confirmed HZ), VE in reduction of clinically significant worst pain, humoral immune responses (anti-gE antibody) and safety and reactogenicity.

From 30 days following dose 2, 49 confirmed cases of HZ were reported in the mTVC of the HZ/su group (N=870) and 135 confirmed cases of HZ were reported in the mTVC of the placebo group (N=851), resulting in an HZ incidence rate of 30.0 per 1,000 PY in the HZ/su group and 94.3 per 1,000 PY in the placebo group. Of 184 confirmed HZ cases, 83.7% were confirmed by PCR and 16.3% were confirmed by HZAC. The primary endpoint was met as the lower bound (LB) of the two-sided 95% confidence interval (CI) of VE was above 0% [VE: 68.2% (95% CI: 55.6%, 77.5%)] after an approximate median follow-up time of 21 months. Although not powered to do so, VE was demonstrated in subgroups of interest, including those 18 – 49 YOA [71.8% (95% CI: 38.8%, 88.3%)] and ≥50 YOA [67.3% (95% CI: 52.6%, 77.9%)] and individuals with multiple myeloma [72.6% (95% CI: 54.8%, 83.7%)] and other underlying diagnoses [63.6% (95% CI: 42.3%, 77.7%)]. VE was not statistically significant when analyzed in 353 subjects from both groups who received PAT for more than 60 days [37.8% (95% CI: -42.3, 73.4)].

The total vaccinated cohort (TVC), consisting of subjects who received at least one dose of study product analyzed by product received (HZ/su group N=922, placebo group N=924), was

the primary population for the evaluation of safety. Injection site (IS) pain was the most commonly reported solicited local symptom after HZ/su administration. Overall by subject, with both doses considered, any grade (Grade 3/severe) IS pain was reported by 83.9% (11.0%) and 9.3% (0.3%) of subjects in the HZ/su and placebo groups, respectively. Overall by subject, with both doses considered, any grade (Grade 3) IS redness and swelling were reported by 33.4% (3.1%) and 18.6% (1.4%) of subjects in the HZ/su group, respectively. Both redness and swelling were reported by 1.0% of placebo group subjects; Grade 3 redness and swelling were not reported by subjects in the placebo group. The most commonly reported solicited general symptoms of any grade were fatigue, myalgia, and headache reported by 56.4%, 53.7% and 33.5% of subjects in the HZ/su group and 38.0%, 26.2% and 18.6% of subjects in the placebo, respectively. The most commonly reported Grade 3 solicited general symptoms in the HZ/su group were fatigue (7.3%), myalgia (6.2%) and shivering (3.9%); these events were reported by 3.5%, 2.1% and 0.8% of subjects in the placebo group, respectively. Overall by subject, with both doses considered, any grade temperature was reported by 20.3% of subjects in the HZ/su group and 5.6% of subjects in the placebo group. Temperatures above 39.5°C were reported in 0.3% in the HZ/su group and 0.1% in the placebo group. Most solicited general symptoms were reported more frequently and tended to have greater severity after dose 2 as compared to dose 1. The proportions of subjects in the HZ/su group reporting solicited symptoms and Grade 3 solicited symptoms were generally higher in subjects 18 – 49 compared to subjects ≥50 YOA.

Overall, there were no clinically significant differences between treatment groups in the proportions of subjects in the TVC who died, reported SAEs, or reported pIMDs during select time points post-vaccination and during the whole post-vaccination period. Up to 30 days following dose 2, SAEs of pneumonia tended to be reported more frequently in the HZ/su group (1.3%) than in the placebo group (0.7%). Unsolicited AEs (serious and non-serious) were reported at similar proportions between the two treatment groups in the 30 days post-vaccination. There were no clinically relevant differences in the proportion of subjects with investigator reports of relapse or progression of their underlying disease between treatment groups at select time points during the study.

Zoster-039: Zoster-039 was an observer-blind, randomized, placebo-controlled trial to assess the safety and immunogenicity of HZ/su. The study enrolled 562 adults diagnosed with a hematologic malignancy who had recently received (within 10 days to 6 months) or were currently receiving immunosuppressive cancer therapy. PAT with activity against HZ was allowed. Individuals were excluded if they were diagnosed with chronic lymphocytic leukemia (CLL) and were not receiving intravenous cancer therapy, had a planned HCT, or had varicella or HZ or vaccination against varicella or HZ within the previous 12 months. Safety and immunogenicity were assessed for 12 months following the last dose of vaccine. Co-primary objectives included safety and humoral immunogenicity [anti-gE antibody vaccine response rate (VRR) and geometric mean concentration (GMC) ratio] in all subjects excluding those with CLL and non-Hodgkin B cell lymphoma. Secondary analyses included an evaluation of confirmed HZ incidence. Following study completion, the Applicant performed a post hoc analysis of VE in the prevention of HZ based on the mTVC.

At study end, after one year of follow-up, the numbers of confirmed cases of HZ in the mTVC were 6 in the HZ/su group (N=283) and 19 in the placebo group (N=279), resulting in HZ incidence rates following dose 1 of 20.2 per 1,000 PY in the HZ/su group and 70.9 per 1,000 PY in the placebo group. In a post hoc analysis of VE, excluding cases which occurred prior to 30 days following dose 2, the VE was 87.2% (95% CI: 44.2%, 98.6%) after a median follow-up time of 11 months. Incidence after 30 days post-dose 2 was 8.5 per 1,000 PY in the HZ/su group and 66.2 per 1,000 PY in the placebo group. Of 16 confirmed HZ cases occurring after 30 days post-

dose 2, 13 (81.3%) were confirmed by PCR and 3 (18.7%) were confirmed by HZAC. The co-primary objectives evaluating VRR and GMC ratio of anti-gE antibody (Ab) response in subjects without CLL and without non-Hodgkin B cell lymphoma (NHBCL) in HZ/su group compared to the placebo group were met.

The TVC (HZ/su group N=283, placebo group N=279) was the primary population for the evaluation of safety. IS pain was the most commonly reported solicited local symptom after HZ/su administration. Overall by subject, with both doses considered, any grade (Grade 3) pain was reported by 79.5% (10.4%) of subjects in the HZ/su group and 16.4% (0%) of subjects in the placebo group. IS redness and swelling, any grade and Grade 3, were reported by similar proportions of subjects in the HZ/su group as reported in Zoster-002. The most commonly reported solicited general symptoms of any grade (Grade 3) overall by subject with both doses considered were fatigue, myalgia, and headache reported by 58.3% (8.3%), 43.9% (7.9%), and 41.4% (4.3%) of subjects in the HZ/su group and 37.2% (3.6%), 17.5% (1.8%), and 23.4% (2.2%) of subjects in the placebo group. Overall by subject, with both doses considered, any grade temperature was reported by 24.5% of subjects in the HZ/su and 7.7% of subjects in the placebo groups. Temperatures above 39.0°C were reported in 1.1% in the HZ/su group and 0.4% in the placebo group. Similar trends in reactogenicity by age and dose number were seen in Zoster-039 as in Zoster-002.

Overall, there were no clinically significant differences between treatment groups for the proportions of subjects in the TVC who died or reported pIMDs, SAEs, or relapse or progression of their underlying malignancy up to 30 days and up to 365 days post-vaccination, or in unsolicited AEs reported in the 30-day post-vaccination period. Up to 30 days following dose 2, SAEs of pneumonia and febrile neutropenia tended to be reported more frequently in the HZ/su group than in the placebo group (pneumonia: 2.0% and 0.4%, respectively; febrile neutropenia: 2.5% and 0.7%, respectively).

The Applicant submitted data from four randomized, observer-blind, placebo-controlled trials of HZ/su in adult IC populations, which CBER considered supportive of the overall safety and effectiveness in a variety of IC populations. Zoster-041 evaluated the safety and immunogenicity of two doses of HZ/su in 264 adult subjects (TVC: N=132 in the HZ/su group, N=132 in the placebo group) with a renal transplant 4 – 18 months prior to their first vaccination and who were on chronic anti-rejection immunosuppressive therapy, excluding individuals with unstable renal function or at increased risk of rejection. Zoster-028 evaluated the safety and immunogenicity of two doses of HZ/su in 232 adults with a solid tumor malignancy (TVC: N=117 in the HZ/su group, N=115 in the placebo group), who were planned to receive or were receiving chemotherapy. Zoster-015 was a Phase 1/2 trial that evaluated the safety and immunogenicity of a three-dose series (not the proposed dose schedule) of HZ/su administered at Months 0, 2, and 6 in 123 adults (TVC: N=74 in the HZ/su group, N=49 in the placebo group) with HIV, enrolling subgroups of subjects that were on antiretroviral therapy (ART) with high CD4 (>200), on ART with low CD4 (50-199), and no ART with high CD4 (>500). Zoster-001 was a Phase 1/2 trial that evaluated a two-dose and three-dose schedule of HZ/su (gE/$AS01_B$) and a vaccine consisting of gE with half dose $AS01_B$ (gE/$AS01_E$) compared to placebo in autoHCT recipients (TVC in the pooled safety analysis: N=29 in the HZ/su 2-dose group, N=30 in the HZ/su 3-dose group, N=30 in the placebo group; gE/$AS01_E$ was not included in the pooled safety analysis).

Anti-gE antibody as measured by a validated enzyme-linked immunosorbent assay (ELISA) was the primary immunologic readout. In general, the populations evaluated in the supportive studies demonstrated an immune response based on anti-gE Ab GMCs and VRRs; however,

this was not the case for all subpopulations. With the exception of solicited adverse events which were reported more frequently in the HZ/su group compared to the placebo group, clinically significant differences in other safety outcomes between the HZ/su and placebo were not observed.

CBER considered Zoster-041, Zoster-028, and Zoster-015 supportive of the proposed expansion of the use of HZ/su, while acknowledging the following:

- The studies were not powered to, and did not, evaluate vaccine efficacy against HZ.
- The studies were small in size, which limits the ability to detect uncommon AEs that may potentially be related to receipt of HZ/su in these populations.
- Some pertinent safety outcomes were not evaluated. Specifically, for the renal transplant population, creatinine (as a marker of graft function) and alloimmunity were not systematically evaluated.

Post-vaccination safety assessment methodology was similar across all six studies, enabling pooling across studies to assess for the occurrence of uncommon adverse events. In general, overall proportions of unsolicited AEs, SAEs, and pIMDs were reported at similar rates in both vaccination groups. Arthralgia, influenza like illness, and pneumonia were reported in at least 1% of the HZ/su group at a rate of at least 1.5 times the placebo group within the 30-day post-vaccination period. Numerical imbalances in SAEs of febrile neutropenia were also observed, though potentially related to underlying disease processes and therapies and less likely to be related to vaccination.

Conclusions/Rationale: HZ/su is licensed to prevent HZ in the US in individuals 50 YOA and older regardless of immune competence. Compared to immunocompetent individuals, in general, IC individuals have a higher risk of HZ, and HZ can cause significant and prolonged morbidity in this population. Therefore, an unmet medical need exists for immunocompromised individuals 18 – 49 YOA. In support of expanding the use of HZ/su to immunodeficient or immunosuppressed individuals including those 18 – 49 YOA, the Applicant has submitted results of six clinical trials in five IC populations, representing 1,587 IC subjects who received at least one dose of HZ/su. In Study -002, efficacy was demonstrated in individuals who had recently received an autoHCT; efficacy was also demonstrated during the period of time they were considered to be at highest risk of HZ (one year post-transplant). In another study, -039, the Applicant conducted a post hoc analysis which demonstrated vaccine efficacy in individuals with hematologic malignancies. There is no known correlate of vaccine-mediated protection against HZ. Although the Applicant has selected anti-gE Ab as the primary immunologic readout for the HZ clinical development program, in one subpopulation (non-Hodgkin B cell lymphoma), VE was demonstrated despite a poor post-vaccination anti-gE response.

Similar to the older adult population, the majority of IC subjects in the HZ/su group experienced local and/or general reactogenicity of short duration. Severe reactogenicity was common and within the IC population, reactogenicity was higher in the younger age stratum. Overall, SAEs, deaths, and pIMDs were reported in similar proportions of subjects in HZ/su and placebo groups during select time periods evaluated. Clinically significant numerical imbalances in adverse events that were observed will be included in the prescribing information (PI).

In consideration of broad use of HZ/su for the prevention of HZ in all IC adults at increased risk of HZ, it is acknowledged that IC populations are heterogeneous and HZ/su has not been evaluated in all IC populations, for all safety outcomes, or at the many potential timepoints relative to administration of immunosuppressive therapies. However, the evidence of efficacy in two IC populations at increased risk of HZ, including one population at the time of greatest risk

of HZ (autoHCT), and demonstration of immune responses in three other populations (solid organ tumor, renal transplant, HIV-positive) provide substantial evidence of effectiveness of vaccination in a diverse population of IC adults. These data, together with the safety data accrued from multiple IC populations, support a favorable risk-benefit profile of HZ/su for use in a broad population of IC adults. Routine pharmacovigilance activities are planned by the Applicant for continued assessment of safety. In addition to routine pharmacovigilance, the Applicant plans to evaluate pregnancy outcomes in IC women receiving HZ/su since the new usage population includes women of child-bearing potential.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Vaccine efficacy (VE) in the prevention of herpes zoster (HZ) in demographic subgroups is summarized below for study Zoster-002, which enrolled immunocompromised individuals who had recently (within 50 – 70 days) received an autologous hematopoietic stem cell transplant (autoHCT). The study was not powered to evaluate differences in VE for these demographic groupings, so the clinical significance of any differences noted between groupings in these analyses is unknown. The subjects included in this analysis had a median age of 57 years (age range 18 – 77 years) and were majority male (63%), not American Hispanic/Latino (97%), and White (79%). Because the proportions of subjects in some racial groups were too low to analyze separately, for the purposes of analyzing efficacy and safety by race, CBER asked the Applicant to group them into four broader groupings which included the following subjects and proportions of the enrolled population in parentheses: African (2.2%, African heritage/African American), Asian (16%, Central/South Asian heritage, East Asian heritage, Japanese heritage or Southeast Asian heritage), White (79%, Caucasian/European heritage or of Arabic/North African heritage), and Other (3%, American Indian, Alaskan native, or Other). No Native Hawaiians or Pacific Islanders were enrolled in Zoster-002.

HZ VE by age
VE was comparable between age strata. VE (95% confidence interval [CI]) was 71.8% (38.8%, 88.3%) in subjects 18 – 49 years of age. VE was 67.3% (52.6%, 77.9%) in individuals ≥50 years of age.

HZ VE by gender
The term gender, as opposed to sex, was used in the clinical development program, with the options of male and female. VE was comparable between genders. VE (95% CI) was 77.6% (60.7%, 88.0%) in females and 60.3% (39.4%, 74.5%) in males.

HZ VE by race
VE (95% CI) was 59.5% (41.8%, 72.2%) for White subjects and 94.5% (78.2%, 99.4%) for Asian subjects. HZ VE could not be determined for the subjects of African heritage (0 confirmed HZ reported in the HZ/su group and 4 in the placebo group) or of Other races (2 in the HZ/su group and 3 in the placebo group) due to a low number of HZ cases reported in each vaccination group and a low number of subjects in these subgroups enrolled. The study was not designed to evaluate VE by racial subgroups. Variations in immunosuppressive therapies, prophylactic antiviral therapy (PAT), and underlying disease in subjects enrolled in different regions may contribute to differences observed by race.

HZ VE by ethnicity
VE could not be determined for the ethnic subgroup American Hispanic/Latino due to a low number of HZ cases reported (0 in the HZ/su group and 3 in the placebo group) and a low

number of subjects in these subgroups enrolled. VE (95% CI) was 67.5% (54.5%, 77.1%) in the group who were not American Hispanic/Latino.

Safety analyses by age, gender, race and ethnicity

Safety by demographic subgroups was assessed by combining results of six different trials of HZ/su in five different immunocompromised populations (individuals with recent autoHCT, hematologic malignancies undergoing or recently completed cancer therapy, prior history of renal transplant, solid tumors undergoing cancer therapy, and positive for HIV). Subjects enrolled in these studies had a median age of 57 years (age range 18 – 87 years) and were majority male (62%), not American Hispanic/Latino (96%), and White (77%). The studies were not powered to evaluate differences in safety based on demographic groupings, so the clinical significance of any differences noted between groups in these analyses is unknown. However, there was only minor variability, if any, for the proportions of subjects who reported the various safety events by age, gender, race and ethnicity.

Deaths: The proportion of subjects who died up to 30 days and 365 days following the last vaccination and during the whole post-vaccination period was higher in the ≥50 years of age (YOA) group compared to the 18 – 49 YOA group. There were no clinically relevant differences in deaths between the HZ/su and placebo group within the younger and older age groups. In the HZ/su group, no clinically significant differences were noted among gender, race, and ethnic groups for the proportions of subjects who died up to 30 days and 365 days following the last vaccination and during the whole post-vaccination period.

Serious adverse events (SAEs) and potential immune-mediated diseases (pIMDs): The proportion of subjects who reported SAEs up to 365 days following the last vaccination and during the whole post-vaccination period was higher in the ≥50 YOA group compared to the 18 – 49 YOA group. There were no clinically relevant differences in the proportions of subjects reporting SAEs between the HZ/su and placebo group within the younger and older age groups. In the HZ/su group, no clinically significant differences were noted between age groups for the proportions of subjects who reported pIMDs up to 365 days post-last vaccination. Though limited by a small number of subjects in some demographic subgroups, in the HZ/su group no clear clinically significant differences were identified between genders, and racial and ethnic groups for the proportions of subjects who reported SAEs and pIMDs up to 365 days post-last vaccination.

Unsolicited adverse events (AEs) reported during the 30-day post-vaccination period: In the HZ/su group, females tended to report AEs at a slightly higher rate than males (49.7% and 44.1%, respectively). In the HZ/su group the proportions of subjects reporting unsolicited AEs (serious and non-serious) during the 30-day post-vaccination period by race ranged from 36.7% (African race) to 48.8% (Asian race). No clinically significant differences were noted in the proportions of subjects who received HZ/su and reported unsolicited AEs by age group (18 – 49 or ≥50 YOA) or ethnic group.

Common AEs which were solicited from subjects during the 7-day post-vaccination period: Among HZ/su recipients, the incidences of solicited local and general symptoms were higher in the 18 – 49 YOA group (91.1% and 70.8%, respectively) when compared to the ≥50 YOA group (84.2% and 60.8%, respectively). The proportions of females in the HZ/su group reporting solicited local and general symptoms (89% and 81%, respectively) were higher than males (84% and 73%, respectively). There were no clinically significant differences in the proportions of subjects reporting local and general symptoms by racial group or ethnicity.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.7, 6.1.11.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

HZ, or shingles, is the clinical manifestation of reactivation of the varicella zoster virus (VZV) after an initial infection with VZV, usually in childhood, as varicella (chickenpox). Following the initial infection, VZV establishes latency in the dorsal root or cranial nerve ganglia and upon reactivation commonly manifests as a unilateral, painful vesicular rash along one or, less frequently, overlapping dermatomes that lasts for approximately two to four weeks; the thoracic dermatomes are the most commonly affected, followed by those in the cranial, lumbar and cervical regions. Symptoms, such as pain and allodynia can range from mild to severe. Acute complications of HZ involving various systems and organs may occur in immunocompetent individuals, including, but not limited to bacterial skin superinfection, HZ ophthalmicus, HZ oticus, transverse myelitis, aseptic meningitis, and vasculopathies (Cohen 2013). A common, potentially long-term complication of HZ is post-herpetic neuralgia, or PHN, which is generally defined as neuropathic pain at the site of the rash that persists for more than one month after rash resolution (Lu et al. 2021). In a systematic review of 49 studies, the risk of developing PHN

ranged from 5% to more than 30% overall and between 6% and 45% across studies evaluating PHN incidence in immunocompromised (IC) populations (McKay et al. 2020). As VZV latency is maintained by robust VZV-specific cell-mediated immunogenicity (CMI), alterations in CMI due to immunosenescence, underlying diseases and/or their treatments render the elderly and immunocompromised individuals at higher risk of HZ, severe HZ, protracted HZ, and HZ-related complications (Gagliardi et al. 2016). Immunocompromised individuals, particularly those status post stem cell transplant, may develop severe disseminated disease with visceral involvement (Chen et al. 2014; Petrun et al. 2015; McKay et al. 2020).

It is estimated that 95% of the adults in the United States (US) are latently infected with VZV and are potentially at risk of experiencing HZ (Schmader 2018). As such, approximately 1 million people in the US report HZ per year, with an individual lifetime risk of approximately 30% (Saguil et al. 2017). In a systematic review of 130 studies conducted in 26 countries, the incidence rate of HZ in the general population in North America, Europe and Asia-Pacific ranged from 3 – 5/1000 person-years (PY) with a steep rise in incidence after 50 years of age (YOA); incidence rates were 6 – 8/1000 PY at 60 years and 8 – 12/1000 PY at 60 and 80 YOA respectively (Kawai et al. 2014).

HZ incidence rates are higher for individuals with alterations in immune status due to disease and therapy as compared to rates for immunocompetent individuals; in a study of German claims data from more than 10 million adults, the incidence rate per 1000 PY, was twice as high for immunocompromised patients [11.5 (95% CI: 11.4 – 11.6)] as compared to immunocompetent individuals [5.9 (95% CI: 5.8 – 5.9)] (Schröder et al. 2017). A population based retrospective study using integrated databases in Spain and including data from approximately 4.4 million adults during the years 2009 – 2014 calculated incidence rates of 4.7 and 9.2 per 1000 PY in immunocompetent and immunocompromised individuals, respectively (Muñoz-Quiles et al. 2020). Rates are amongst the highest (40 – 60/1000 PY) in individuals who undergo hematopoietic stem cell transplantation (Sahoo et al. 2017; Schröder et al. 2017; Mao et al. 2018). Rates for adults with solid organ transplants, hematologic malignancies, HIV and other neoplasias (populations evaluated during the HZ/su development program) per 1000 PY were 12.7 (95% CI:11.8 – 13.5), 12.0 (95% CI:11.5 – 12.5), 12.9 (95% CI: 12.0 – 14.0) and 11.0 (95% CI:10.8 – 11.2), respectively (Muñoz-Quiles et al. 2020). As with immunocompetent adults, HZ incidence rates in immunocompromised adults increase with advancing age (Muñoz-Quiles et al. 2020). Other immunocompromised populations are thought to be at increased risk of HZ and HZ complications; more data are needed to inform the burden of disease in these populations. Additionally, more data are needed to characterize risk of HZ and HZ complications in subsets of subjects with particular conditions based on intensity of immunosuppression and by type of therapy, such as Janus kinase inhibitors and proteasome inhibitors, which have been associated with increased incidence of HZ (Chanan-Khan et al. 2008; Curtis et al. 2016; McKay et al. 2020; Sunzini et al. 2020).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Prophylaxis

HZ/su is the only vaccine marketed in the United States with the indication of prevention of HZ. It is approved for use in individuals ≥50 YOA.

Oral acyclovir is indicated for the reduction of mortality and risk of developing herpes virus infections in certain severely immunocompromised patients, namely those with advanced HIV disease or following bone marrow transplantation. Antiviral therapy against VZV is

recommended in a practice guideline for at least one year post allogeneic and autologous stem cell transplant (Tomblyn et al. 2009). Additionally, antiviral prophylaxis has been administered for prevention against VZV reactivation during chemotherapy with select treatments such as protease inhibitors for multiple myeloma (Fukushima et al. 2012) or for certain individuals treated with Janus kinase inhibitors (Nash et al. 2021).

Therapies for HZ and acute HZ-associated pain

Some oral or intravenous antivirals may be administered for HZ or VZV recurrence. Acyclovir, famciclovir and valacyclovir are indicated for use in adults to treat HZ and may be administered orally for uncomplicated cases; the package inserts for famciclovir and valacyclovir state that the efficacy and safety of these drugs has not been established for this indication in immunocompromised patients. Intravenous acyclovir is indicated for the treatment of shingles in immunocompromised patients if lesions are not older than 72 hours. Treatment with antivirals should begin prior to 72 hours after rash onset to optimize benefit such as reducing new lesion formation, hastening rash resolution and decreasing the severity and duration of acute pain (Dworkin et al. 2007; Cohen 2010). It is unclear whether antivirals administered for HZ have an effect on the incidence of PHN.

Acute HZ pain is generally managed in accordance with principles for managing any pain (Schmader 2007). Following the three step World Health Organization pain ladder and incorporating individual considerations (e.g., patient age, co-morbidities, concomitant therapies) may guide systemic analgesic treatment, and tricyclic anti-depressants (e.g., amitriptyline) and anti-epileptics (e.g., gabapentin, pregabalin) have been used to treat the neuropathic component of the acute pain (Werner et al. 2017).

Management of chronic HZ-associated pain

Current recommendations for treating neuropathic pain include gabapentin, pregabalin, duloxetine, venlafaxine and tricyclic antidepressants as first line therapy; however, the efficacy of duloxetine and venlafaxine for treatment of PHN has not been established and is extrapolated from other conditions (Schutzer-Weissmann and Farquhar-Smith 2017). Additional therapies include lidocaine or capsaicin topical therapy, nerve blockade and opioids, although opioid therapy, because of the potential for abuse, is indicated mainly for the treatment of severe acute pain exacerbations (Finnerup et al. 2015).

Reviewer comment: *Recommendations from practice guidelines for the treatment of acute HZ-associated pain and PHN may include therapies that have not been specifically approved for that purpose.*

2.3 Safety and Efficacy of Pharmacologically Related Products

There are no pharmacologically related products marketed in the US.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Herpes zoster subunit vaccine (HZ/su) was approved for use for the prevention of HZ in adults ≥50 YOA in the US in 2017.

As of January 2021, HZ/su is licensed for use in the US, Canada, Japan, Australia, China, New Zealand, Hong Kong, Singapore, and the European Economic Area. Global post-marketing experience includes more than [redacted] doses distributed.

The association between vaccination with HZ/su and Guillain-Barré syndrome (GBS) was evaluated in a post-licensure study using Medicare claims data from October 2017 through February 2020. The risk of GBS following vaccination with HZ/su was assessed in self-controlled case series analyses using a risk window of 1 to 42 days post-vaccination and a control window of 43 to 183 days post-vaccination. The primary analysis (claims-based, all doses) found an increased risk of GBS during the 42 days following vaccination with HZ/su, with an estimated 3 excess cases of GBS per million doses administered to adults aged 65 years or older. The results of this observational study suggest a causal association of GBS with HZ/su, however, the available evidence is insufficient to establish a causal relationship. A labeling supplement to include the information on risk of GBS following HZ/su was approved on March 24, 2021.

gE and $AS01_B$
There are no other US-licensed or investigational products under IND utilizing the GlaxoSmithKline (GSK) VZV glycoprotein E.

There are investigational products under IND which contain the AS01 adjuvant at full ($AS01_B$) or half ($AS01_E$) concentration including vaccines against hepatitis B, HIV, cytomegalovirus, *Streptococcus, Hemophilus influenzae,* malaria and tuberculosis. No safety issues relevant to the current sBLA have been identified from these development programs.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The following list references key milestones in the clinical development program for HZ/su, primarily, but not limited to, those related to IND 13879; the bolded amendment numbers below refer to amendments submitted to that IND. See the reviews written by specific CBER disciplines for discussions about other components of the development plan relevant to this sBLA such as assay validation reports and statistical plans.

28 APR 2008	A pre-IND meeting was held to discuss the Applicant's plan to initiate US development of HZ/su for prevention of HZ in healthy adults. At the time, CBER recommended that studies in healthy and immunocompromised adults be conducted under separate INDs.
24 OCT 2008	Submission of IND 13857, initiating the clinical development of HZ/su in healthy older adults ≥50 YOA, was received by CBER.
18 DEC 2008	Submission of IND 13879 **(Amendment 0)** contains supportive pharmacology, toxicology, and chemistry, manufacturing and controls information as well as available results from exploratory non-IND clinical studies of the gE vaccine which were also cross-referenced to IND 13857. The amendment includes a protocol for Zoster-001, a Phase 1/2a, randomized, placebo-controlled, observer-blind study to evaluate the safety and immunogenicity of HZ/su when administered as two or three doses to adults status post autologous HCT (autoHCT).
25 JUN 2010	**Amendment 17** contains the final protocol for Zoster-015, a Phase 1/2a, randomized, placebo-controlled, observer-blind study of the safety and immunogenicity of HZ/su when administered as 3 doses to HIV-infected adult subjects.
18 AUG 2011	**Amendment 32** contains meeting background materials for an end of phase 2 (EOP2) meeting and a concept protocol for Zoster-002, a Phase 3, randomized, placebo-controlled clinical endpoint efficacy study of HZ/su when administered to adult subjects status post autoHCT. As enumerated in the meeting background

materials, approximately 4000 immunocompromised adults would receive HZ/su in the planned clinical development program, which included three efficacy studies (enrolling HIV-infected adults, adults with hematologic malignancies and adults status post autoHCT) and two safety and immunogenicity studies (enrolling adults with solid organ malignancies and corticosteroid immunosuppression). Results of an interim analysis of safety and immunogenicity from Zoster-001 were provided in the materials to support initiation of Zoster-002.

21 SEP 2011 An end of phase 2 (EOP2) teleconference after CBER sent written responses to the Applicant's questions including, but not limited to concurrence that the safety and immunogenicity results from Zoster-001 supported further evaluation of the vaccine in the autologous transplant population and agreement with the proposed regimen of two doses of vaccine, with the first dose administered approximately 60 days post-transplant. CBER also agreed with the proposed primary objective and endpoint of study Zoster-002 and the sample size of the study but asked that the Applicant power the study for a LB of the 95% confidence interval for VE of 25%.

15 MAR 2012 Following review of updated and tracked changes version of the revised Zoster-002 concept protocol submitted in **Amendments 41 and 44**, CBER's comments to the Applicant included: asking for confirmation that an end-of-study analysis would be performed, requesting an analysis of VE when all evaluable subjects reached one year post-transplant, reiterating a request for a LB of the 95% CI for VE to be 25%, and requesting an analysis of PHN VE in subjects with confirmed HZ. CBER also disagreed with the proposed plan to accumulate 1200 person years of safety follow-up and requested that each subject have a minimum of one year of safety follow up.

27 MAR 2012 The Applicant submitted a final version of the protocol for Zoster-002 incorporating the following changes based on CBER's comments of 15-MAR-2012 in **Amendment 52**. In response to CBER comments, they stated that: an end of study analysis would be conducted if the final triggered analysis occurred prior to study end, VE efficacy would be analyzed when all subjects had reached at least one year post hematopoietic stem cell transplant (HCT), although the LB of the 95% CI of VE would remain unchanged, the study would be powered for a LB of >25%, a new study objective related to PHN VE in subjects with confirmed HZ was added, and the conditions for final triggered analysis would include all subjects need to have completed Visit 4.

08 JUN 2012 **Amendment 58** contains meeting background materials to inform discussion about the adequacy of the current clinical data package to support initiation of a Phase 3 study in adults with hematologic malignancies (Zoster-039), CBER's input on key elements of the proposed study design (including but not limited to study endpoints, duration, population, sample size, statistical methodology) for Zoster-039 as well as advice regarding potential conversion of the study from a safety and immunogenicity study to a pivotal efficacy study. The Applicant's clinical development plan at the time included Zoster-038, a Phase 3 safety/immunogenicity and early efficacy study with a similar optional conversion into a pivotal efficacy study.

13 JUL 2012 The Type C meeting regarding Zoster-039 was held. CBER agreed that the available clinical data package supported initiation of the study. There was also agreement on general study design with potential adaptation to a clinical disease endpoint efficacy study but CBER recommended subgroup enrollment by underlying disease be reflective of the hematologic malignancy population.

21 DEC 2012 **Amendment 73** contains the Applicant's request for a Type B EOP2 meeting to discuss the results of Zoster-015 and a planned study design for a Phase 3 study in the same population (HIV infected individuals).

30 JAN 2013 **Amendment 77** contains a new protocol for Zoster-028, a Phase 2/3 study to evaluate the safety and immunogenicity of HZ/su when administered to adults with solid tumors receiving chemotherapy.

30 JAN 2013 **Amendment 78** contains a new protocol for Zoster-041, a Phase 3 study to evaluate the safety and immunogenicity of HZ/su when administered to adults with renal transplant.

06 FEB 2013 **Amendment 79** contains meeting background materials for a Type B EOP2 meeting to inform a discussion about a proposed Phase 3 efficacy study (Zoster-038) enrolling approximately 1408 adults infected with HIV. The Applicant also informed CBER of their plan to request a waiver of pediatric studies in immunocompromised children <1 year of age and a deferral of pediatric studies for children from 1 – 17 years of age and request CBER input on their plans.

26 FEB 2013 **Amendment 84** contains a request to withdraw the Type B meeting referred to in Amendment 79.

29 OCT 2013 **Amendment 104** contains the final study protocol for Zoster-038.

07 MAR 2014 **Amendment 113** contains reference to a submission under IND 13857 Amendment 125 to discuss the Targeted Product Profile and updated clinical development plan for HZ/su.

29 APR 2015 An initial pediatric study plan (iPSP) was submitted to the IND in **Amendment 144**. The Applicant stated plans to request a full waiver of studies in all pediatric age groups.

09 OCT 2015 A revised iPSP (Agreed iPSP) incorporating CBER comments was submitted to **Amendment 157**.

26 JUN 2016 An agreed iPSP was presented to the Pediatric Review Committee (PeRC). The PeRC agreed with the Applicant's plan to request a full waiver of studies in all pediatric populations due to the impracticability or impossibility of conducting clinical endpoint studies in the US because the incidence of HZ in the pediatric population is low and cases are widely dispersed.

20 OCT 2017 HZ/su (Zoster vaccine recombinant, adjuvanted) is licensed for use by FDA for prevention of HZ in adults ≥50 years of age.

22 MAY 2018 A briefing document was submitted by the Applicant to IND 13857 Amendment 321 to inform a meeting about extension of the indication of prevention of HZ in all adults ≥18 YOA.

11 JUL 2018 A Type C meeting was held to discuss questions (submitted to IND 13857, Amendments 317 and 321) regarding expansion of the indication for HZ/su to adults ≥18 YOA at risk of HZ and the statistical validation of a Correlate of Protection or CoP (the CoP analysis was submitted to IND 13857 Amendment 316). The wording of the extended indication was discussed. CBER noted that the CoP analysis was not sufficient to demonstrate that anti-gE antibody (Ab) concentrations at one month after a second dose was adequately validated to predict vaccine-mediated protection against HZ.

22 AUG 2019 **Amendment 220** contains a protocol for Zoster-073, an open-label extension study of Zoster-041 to evaluate long term immunogenicity (4 – 7 years) after initial vaccination with a two-dose series of HZ/su and the safety and immunogenicity of revaccination with two additional doses of HZ/su when administered to adults status post renal transplant.

20 DEC 2019 **Amendment 223** contains the Applicant's responses to a CBER information request (IR) of 29-AUG-2019 regarding post-vaccination study monitoring and

	results of anti-major histocompatibility complex (MHC) antibody, biopsy-proven rejection results and HZ case narratives from the Zoster-041 study.
03 FEB 2020	**Amendment 225** contains the Applicant's responses to CBER's IR of 19-NOV-2019 regarding Zoster-028 and Zoster-039. The Applicant responded to queries about Zoster-028 concerning immune responses to vaccine in the OnChemo group, the immune responses to vaccination in subjects who reported suspected HZ, and information about a subject who reported a non-serious case of tachycardia immediately after first vaccination. The Applicant responded to queries about Zoster-039 which included information about demographics (including but not limited to numbers and proportions of subjects on antiviral therapy and B cell depletion therapy in the study), fatal SAEs and narratives of confirmed HZ cases.
05 FEB 2020	A pre-BLA meeting was held, referencing meeting materials submitted on 05-DEC-2020 in **Amendment 221** (meeting summaries can be found in **Amendment 228**)**.** Pooling of safety data across studies and the format of datasets to be submitted were among items of discussion; CBER requested that the Applicant submit an analysis of pooled safety data across studies in addition to the analysis of safety data from each study.
24 MAR 2021	A labeling supplement to the BLA with FDA-required updates to the "Warnings and Precautions" and "Adverse Reactions" sections of the Package Insert to include new safety information about Guillain Barre Syndrome following vaccination with HZ/su was approved.
08 JUN 2021	For the current supplement which includes a new dosing regimen for immunodeficient or immunosuppressed individuals, the PeRC agreed with the Applicant's request for a full waiver of studies in all pediatric age groups. The PeRC agreed with granting a full waiver of required pediatric assessments based on the statutory reason that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients.

2.6 Other Relevant Background Information

Not applicable.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. Datasets inadvertently omitted from the original submission were submitted in a timely fashion. See section 5.2 for a listing of sBLA submission.

The Applicant submitted their analysis datasets in legacy format and also submitted Study Data Tabulation Model (SDTM) datasets for the six individual trials and the integrated summary of safety (ISS). This approach was agreed to in communications surrounding the original BLA After Action Review on April 16, 2018, and the pre-BLA Meeting on February 5, 2020. In 125614/398.2, the Applicant clarified that the SDTM datasets were created using a legacy data conversion process. The legacy datasets were populated with data collected on case report forms as well as data provided electronically from laboratories. Then a structured validated process was undertaken to convert the legacy data format to SDTM. Data that was not available in each of the SDTM datasets included subject age (as day may not have been collected and

age would require derivation) and protocol deviations (due to differences in procedures for collecting and extracting the data). The clinical review of the data is based on the analysis datasets in legacy format.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Of the six trials submitted, four were conducted under IND – the two trials for which efficacy was evaluated, Zoster-002 and Zoster-039, and two additional trials, Zoster-015 and Zoster-001. Zoster-028 and Zoster-041 were conducted according to 21 CFR 312.120, foreign clinical studies not conducted under a US IND.

The Applicant states that all trials were approved by Independent Ethics Committees and conducted in accordance with the principles of good clinical practice (GCP) and all applicable regulatory requirements, including the Declaration of Helsinki. Written informed consent was obtained from all subjects as per GCP requirements.

During the conduct of all of the submitted studies, the Applicant identified no significant deviations from GCP compliance.

3.3 Financial Disclosures

The Applicant made reasonable efforts to obtain financial disclosure from all investigators and sub-investigators who participated in the studies submitted to the BLA.

Under “Significant Payments of Other Sorts from the Sponsor of the Covered Study [21 CFR 54.4(a)(3)(ii), 54.2(f)]”, the Applicant listed one Principal Investigator for Zoster-002 study whose site contributed 2.72% of the total recruitment for the study. The Applicant states that study statisticians determined there was no potential impact to the study. The Applicant listed no investigators as having proprietary interest in the tested product [21 CFR 54.4(a) (3) (iii), 54.2(c)] or having significant equity interest in the Sponsor of the study product [21 CFR 54.4(a)(3)(iv), 54.2(b)].

Reviewer comment: *The financial disclosure forms from investigators and sub-investigators were reviewed by CBER, and there was no indication that any missing information or disclosed financial arrangements would impact the overall integrity of the data submitted.*

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

There were no CMC related changes requested by the Applicant in this submission.

4.2 Assay Validation

Evaluation of the effectiveness of HZ/su for this sBLA was based on the results of analyses of vaccine efficacy in the prevention of clinical disease, with supportive data on immune responses to HZ/su in IC populations. CBER assay reviewers confirmed that the immunologic assays used in the development program were adequately validated for their intended use to evaluate immune responses to vaccination. Immunoassays were reviewed at the time of the original BLA and no changes to the assay since the approval.

Reviewer comment: *Please refer to the CBER CMC review.*

4.3 Nonclinical Pharmacology/Toxicology

Nonclinical studies submitted in the original BLA included a developmental and reproductive toxicity (DART) study of gE/AS01$_B$ in rats. Female rats received 0.2 mL, 2/5th the human dose of HZ/su or the AS01$_B$ adjuvant alone by intramuscular (IM) injection on gestation Days 3, 8, 11, and 15, and on lactation Day 7. No adverse effects on pre-weaning development up to post-natal Day 25 were observed. No vaccine-related fetal malformation or variations were observed.

At the recommendation of the European Medicines Association Committee for Medicinal Products for Human Use, for extension of the indication to women of childbearing potential, a DART study in another species (rabbits) with full human doses of the AS01$_B$ adjuvant was performed and submitted in this sBLA. The study was conducted to investigate the potential influence of a full human dose of AS01$_B$ on fertility parameters, embryo-fetal pre- and post-natal survival, and development of the offspring. [redacted] rabbits received saline, a non-HZ, non-US-licensed vaccine, or AS01$_B$ (0.5 mL/injection, full human dose) by intramuscular injection 28 days prior to mating, 14 days prior to mating, on Gestation Day (GD) 3, 11, 16, and 24, and after natural delivery on lactation day (LD) 7. Mated females and their litters were euthanized on GD 29 (cesarean section cohort) or on LD 35 (natural delivery cohort). Three rabbits in the AS01$_B$ group were found dead on GD 31, LD 28, and LD 30 showing reduced food consumption with body weight loss. The cause of death could not be determined; the mortality rate was above the submitted historical control data. There were no AS01$_B$-related effects on clinical signs, dermal observations, or necropsy observations in the dams. There were no AS01$_B$-related effects on mating and female fertility, embryo-fetal pre- and post-natal survival, growth, or development. No adverse effects on pre-weaning development up to post-natal Day 35 were observed.

Reviewer comment: *In the above study, the cumulative dose of AS01$_B$ after 7 administrations was greater than the cumulative human dose. The toxicologic assessment of the findings in the nonclinical studies and discussions between the toxicology review team and office management resulted in a determination that a follow up DART study is not necessary in light of the proposed post-marketing observational clinical study to assess pregnancy outcomes when HZ/su is administered to immunocompromised pregnant women. Please see the toxicologic review for further details.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

AS01$_B$ adjuvant induces a local and transient activation of the innate immune system by two immune enhancers: monophosphoryl lipid A (MPL) and QS-21. MPL, a purified derivative of the lipopolysaccharide component of the cell wall of Salmonella enterica, signals through Toll-like Receptor 4, directly activating dendritic cells (Wang et al. 2020). QS-21 is a triterpene glycoside isolated from the [redacted] of the *Quillaja saponaria* tree that induces a balanced Th1/Th2 immune response; multiple mechanisms of action may contribute to its adjuvant effect (Lacaille-Dubois 2019; Wang 2021). The two agonists activate antigen presenting cells loaded with antigen in the draining lymph node which enables recruitment of naïve CD4+ T cells; studies performed by the Applicant indicate that co-localization of both MPL and QS-21 are required to induce the

maximal frequencies of gE-specific cytokine-producing CD4+ T cells and the highest titers of gE specific antibodies.

4.5 Statistical

The statistical reviewer verified that the primary study endpoints of Zoster-002, Zoster-039 were supported by the submitted data. Please refer to the CBER statistical reviewer's memo for details.

4.6 Pharmacovigilance

The Applicant's current pharmacovigilance plan is similar to ongoing pharmacovigilance initiated at the time of licensure. The potential risks of pIMD and ocular complications post-vaccination are addressed by supplementing routine pharmacovigilance with enhanced surveillance and active surveillance. Enhanced surveillance consists of generating background rates for conditions of interest, conducting observed to expected analyses using passive surveillance data from routine pharmacovigilance, and utilizing follow-up questionnaires to gather data systematically for reported cases of conditions of interest. Enhanced surveillance occurs for the following events: polymyalgia rheumatica, rheumatoid arthritis, psoriasis, autoimmune thyroiditis, multiple sclerosis, Guillain-Barré syndrome, idiopathic thrombocytopenia, optic neuritis, inflammatory bowel diseases, Still's disease adult onset, leukocytoclastic vasculitis, gout, optic ischemic neuropathy, temporal arteritis, and inflammatory, non-infective ocular disease. Active surveillance consists of two Targeted Safety Study PMCs, EPI-Zoster-030, in adults ≥50 YOA, and EPI-Zoster-032, in the Medicare population (≥65 YOA).

As the use of HZ/su in pregnant or lactating women has not been prospectively studied during the development program, at CBER's recommendation, the Applicant agreed to a post-marketing commitment (PMC) study to evaluate HZ/su administered in pregnancy, EPI-Zoster-039 (See sections 9.1.1).

At the time the clinical review was finalized, the pharmacovigilance reviewer had not identified any major issues with the Applicant's proposal.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Joint review responsibilities
Dr. Darcie Everett reviewed the individual clinical trials Zoster-002, Zoster-039, as well as the pooled analyses. Dr. Paula Agger participated in the review of Zoster-028 and Zoster-041 and provided background and expertise regarding the clinical development of HZ/su. The clinical study reports (CSRs) for Zoster-001 and Zoster-015 were reviewed during the original BLA submission, and the data from those studies were reviewed in this sBLA as part of the pooled IC safety population.

Approach to clinical review of pivotal studies and pooled data
The six submitted clinical studies evaluated HZ/su in five IC populations, which are unique in terms of type of immunocompromise, medications, morbidity and mortality, risk of HZ, and disease-specific risk factors that have the potential to be affected by or limit the effectiveness of HZ/su. CBER requested an integrated analysis of safety in order to better identify any safety concerns, for example for the analysis of rare events such as potential immune-mediated diseases (pIMDs).

Vaccine efficacy was evaluated as a pre-specified endpoint in one of the six trials and as a post hoc analysis in one additional trial. The Applicant did not analyze pooled efficacy data due to the heterogeneity of the patient populations, underlying diseases, treatment profiles, and the dominant size of Zoster-002.

The coding dictionary for the ISS dataset used Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. CBER conducted analyses, not provided by the Applicant, that utilized safety review tools to evaluate safety data by MedDRA hierarchies and Standardized MedDRA Queries (SMQs) (utilizing a safety analytic software tool developed by FDA). Unless otherwise noted, SMQ analyses are based on the narrow SMQ. Comparative analyses were based on the individual studies utilizing previous versions of MedDRA or on the ISS dataset using MedDRA version 22.1, even when analyzing the individual studies.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The sBLA documents that served as the basis for the clinical review are presented below. Cover letters for each amendment were also reviewed. For the IND documents (under INDs 13857 and 13879) that served as a reference, please see section 2.5.

- 125614/398.0: (September 24, 2020) Modules 1.2 (Cover Letter and Note to the Reviewer), 1.3 (Administrative information, including Debarment Certification and Financial Disclosure), 1.6 (Meetings), 1.9 (Pediatric Administrative information), 1.14 (Labeling), 1.16 (Risk Management Plan), 2.2 (Introduction), 2.5 (Clinical Overview), 2.7 (Clinical Summary), 5.2 (Tabular Listing of all Clinical Studies), 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication), 5.3.5.3 (Reports of Analyses of Data from More than One Study), 5.3.6 (Reports of Postmarketing Experience)
- 125614/398.1: (October 2, 2020) Module 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication) – Zoster-041 SDTM datasets inadvertently omitted from initial sBLA submission.
- 125614/398.2: (December 24, 2020) Modules 1.11.3 (Efficacy Information Amendment – responses to IR sent December 4, 2020 on IC indication), 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication) – regarding applicability of foreign data, legacy and tabulation datasets, resubmission of Zoster-041 analysis datasets, and list of investigators, IEC/IRB for Zoster-002 and Zoster-039
- 125614/398.3: (January 29, 2021) Module 1.11.3 (Clinical Information Amendment – Responses to IR received January 15, 2021) – regarding legacy and tabulation datasets.
- 125614/398.4: (February 26, 2021) Module 1.11.3 (Clinical Information Amendment – Responses to IR received February 12, 2021) – regarding legacy and tabulation datasets.
- 125614/398.5: (March 1, 2021) Module 1.11.3 (Clinical Information Amendment – Responses to IR received January 29, 2021) – regarding applicability of foreign data.
- 125614/398.7: (April 1, 2021) Module 1.11.3 (Clinical Information Amendment – Responses to IR received March 12, 2021) – regarding postmarketing evaluation in pregnancy
- 125614/398.8: (April 5, 2021) Module 1.14 (Labeling) – regarding updated prescribing information (PI) with information on a postmarketing observational study evaluating risk of Guillain Barre syndrome (GBS).
- 125614/398.9: (May 6, 2021) Module 1.11.3 (Clinical Information Amendment – Responses to IR received April 22, 2021) – regarding analysis of efficacy by select

subgroups, clinical events, subject disposition, and reason for treatment discontinuation in Zoster-002 and Zoster-039.

- 125614/398.10: (May 14, 2021) Module 1.11.3 (Clinical Information Amendment – Corrected responses to IR received March 12, 2021, Responses to IR received April 13, 2021, and Concept protocol) – regarding PMC observational safety study to evaluate pregnancy exposures, 1.16 (Risk Management Plan).
- 125614/398.11: (June 14, 2021) Module 1.11.3 (Clinical Information Amendment – Responses to IRs received June 7, 2021 and June 9, 2021) – regarding efficacy by race, immunogenicity tables including multiple studies, analysis of disease progression in Zoster-002, SAEs in Zoster-039, and calculation of VE for reduction of duration of severe worst pain.
- 125614/398.12: (June 21, 2021) Module 1.11.3 (Clinical Information Amendment – Responses to IR received June 7, 2021) – regarding pIMDs.
- 125614/398.13: (June 28, 2021) Modules 1.11.3 (Clinical Information Amendment – Additional analyses to support labeling), 1.14 (Labeling)
- 125614/398.15: (July 13, 2021) Modules 1.11.3 (Clinical Information Amendment – Additional analyses to support labeling), 1.14 (Labeling)
- 125614/398.16: (July 19, 2021) Modules 1.11.3 (Clinical Information Amendment – Responses to IR received July 14, 2021) – regarding revised PMC safety study dates, 1.14 (Labeling)
- 125614/398.17: (July 21, 2021) Module 1.14 (Labeling)
- 125614/398.18: (July 22, 2021) Module 1.14 (Labeling)

Reviewer comment: *Information requests from CBER were adequately addressed by the Applicant.*

5.3 Table of Studies/Clinical Trials

Table 1. Overview of Clinical Studies Included in the Safety Pooling Analyses

Study ID	Zoster-002	Zoster-039	Zoster-028	Zoster-041	Zoster-015	Zoster-001
IND/non-IND and US Study Sites	IND US: Yes	IND US: Yes	Non-IND US: No	Non-IND US: No	IND US: Yes	IND US: Yes
Study Design and Purpose*	Phase 3, randomized, observer-blind, placebo-controlled study Evaluate VE for prevention of HZ (pivotal clinical endpoint study)	Phase 3, randomized, observer-blind, placebo-controlled study Safety and humoral immunogenicity, VE for prevention of HZ added post hoc	Phase 2/3, randomized, observer-blind, placebo-controlled study Safety and humoral immunogenicity	Phase 3, randomized, observer-blind, placebo-controlled study Safety and humoral immunogenicity	Phase 1/2a, randomized, observer-blind, placebo-controlled study Safety and humoral and cellular immunogenicity	Phase 1/2a, randomized, observer-blind, placebo-controlled study Safety and humoral and cellular immunogenicity
Population	autoHCT recipients ≥18 YOA, two subgroups by underlying disease (minimization factor): Multiple myeloma and Other	Adults ≥18 YOA with hematologic malignancies, stratified to three subgroups by underlying disease: NHBCL, CLL, MM/other diseases	Adults ≥18 YOA with solid tumors treated with chemotherapy	Renal transplant recipients ≥18 YOA	HIV-infected adults ≥18 YOA Divided into 3 cohorts by HIV status: • Antiretroviral therapy (ART) High CD4 cohort • ART Low CD4 cohort • Non-ART High CD4 cohort	autoHCT recipients ≥18 YOA
Schedule	2 doses (Months 0 and 1-2)	2 doses (Months 0 and 1-2)	2 doses (Months 0 and 1-2)	2 doses (Months 0 and 1-2)	3 doses (Months 0, 2, and 6)	3 doses (Months 0, 1, and 3)

Study ID	**Zoster-002**	**Zoster-039**	**Zoster-028**	**Zoster-041**	**Zoster-015**	**Zoster-001**
Treatment groups TVC N (%)	1. HZ/su TVC N=922 (49.9%) 2. Placebo TVC N=924 (50.1%)	1. HZ/su TVC N=283 (50.4%) 2. Placebo TVC N=279 (49.6%) Subjects vaccinated either during or after cancer therapy	1. HZ/su TVC N=117 (50.4%) Pre-chemo: 90 On chemo: 27 2. Placebo TVC N=115 (49.6%) Pre-chemo: 91 On chemo: 24	1. HZ/su TVC N=132 (50.0%) 2. Placebo TVC N=132 (50.0%)	1. HZ/su TVC N=74 (60.2%) 2. Placebo TVC N=49 (39.8%)	1. 3-dose HZ/su TVC N=30 (25.0%) 2. 2-dose HZ/su: 1 dose of Placebo at Month 0+2 doses of HZ/su at Months 1 and 3 TVC N=31 (25.8%) 3. 3-dose gE/AS01$_E$ TVC N=29 (24.2%)[†] 4. 3-dose Placebo TVC N=30 (25.0%)
Follow-up Time	Median 21-month	12 months after last dose	12 months after last dose	12 months after last dose	12 months after last dose	12 months after last dose
Subjects from US N (%)	250 (13.5%)	23 (4.1%)	0	0	42 (34.1%)	89 (100%)
Number of Subjects 18 – 49 YOA by group	HZ/su: 230 Placebo: 229	HZ/su: 74 Placebo: 73	HZ/su: 31 Placebo: 30	HZ/su: 48 Placebo: 49	HZ/su: 46 Placebo: 34	HZ/su: 14 Placebo: 4

Source: Adapted from 125614/398.0, ISS, Table 1, pp. 62 – 68
HZ/su = "Shingrix" (gE antigen and AS01$_B$ adjuvant); TVC = total vaccinated cohort; N = Total number of subjects in a group
[*] Study phase is Applicant's description
[†] The gE/AS01$_E$ 3-dose group from Zoster-001 was not included in the pooled safety analysis (section 8). Subjects in the three-dose HZ/su, two-dose HZ/su, and placebo groups were included. For the two-dose HZ/su group, only subjects who received at least 1 dose of HZ/su were included in the TVC in the pooled analysis. Two out of 31 subjects in this group received only dose 1 (placebo), did not receive a dose of HZ/su, and hence, 29 subjects are included in the pooled analysis. The safety and reactogenicity data reported in the two-dose HZ/su group during the period from administration of dose 1 (placebo) to administration of dose 2 (gE/AS01$_B$) were not included in this analysis as subjects received placebo. HZ/su doses received at Month 1 and 3 for this group were considered as dose 1 and dose 2 vaccinations.

5.4 Consultations

At the time of the original BLA, the Applicant requested and was granted a full waiver of studies in all pediatric age groups. The statutory rationale for the full waiver [see Section 505B(a)(5)(A)(i) of the Food, Drug and Cosmetic Act] was that it was impossible or highly impracticable to conduct clinical endpoint studies to evaluate the use of HZ/su in the United States pediatric population because the estimated annual number of cases is low and widely dispersed across the United States. This sBLA triggered PREA due to the addition of a new dosing regimen (Month 0 and 1 – 2 to allow for more flexibility in vaccinating the IC population). CBER supported the Applicant's request for a full waiver of studies for the new dosing regimen in all pediatric age groups and recommended that the most appropriate statutory reason for requesting the waiver is that the drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients. On June 8, 2021, the PeRC agreed with the Applicant's request for a full waiver of the pediatric assessment of the new dosing regimen of HZ/su.

Reviewer comment: *Vaccination against varicella is part of the routine pediatric vaccination schedule in the US. The incidence of HZ in children is low, and HZ incidence in vaccinated children is lower than in unvaccinated children, even in pediatric IC populations (Weinmann et al. 2013). A majority of IC children will likely have been vaccinated prior to the onset of immunocompromise. For these reasons CBER recommended the above rationale for the full waiver.*

5.4.1 Advisory Committee Meeting

An Advisory Committee meeting was held at the time of the review of the original BLA, on September 13, 2017. CBER determined that no additional input from an Advisory Committee was needed to make a benefit:risk assessment regarding extension of the use of HZ/su to include immunocompromised persons 18 – 49 YOA.

5.5 Literature Reviewed

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

Zoster-002 was a Phase 3, randomized, observer-blind, placebo-controlled, multicenter, clinical trial designed to assess the prophylactic efficacy, safety, and immunogenicity of HZ/su when administered intramuscularly on a two-dose schedule to adult autologous hematopoietic stem cell transplant (autoHCT) recipients.

Study dates
Study initiation date: July 13, 2012
Study completion date: February 1, 2017

6.1.1 Objectives

Primary objective

- To evaluate VE in the prevention of HZ in autoHCT recipients ≥18 YOA;

Secondary objectives

- To evaluate VE in reducing the total duration of 'worst' HZ-associated pain over the entire pain reporting period in autoHCT recipients ≥18 YOA with confirmed HZ
- To evaluate VE in the reduction of confirmed HZ-associated complications in autoHCT recipients ≥18 YOA
- To evaluate VE in the prevention of PHN in autoHCT recipients ≥18 YOA
- To evaluate humoral immune responses to the study vaccine when administered according to a two-dose schedule in a sub-cohort of subjects
- To evaluate vaccine safety and reactogenicity in autoHCT recipients ≥18 YOA

Select tertiary objectives

- To evaluate VE in the prevention of HZ in autoHCT recipients ≥18 YOA when all subjects reach one-year post HCT
- To evaluate VE in the prevention of PHN in autoHCT recipients ≥18 YOA with confirmed HZ
- To evaluate VE in reducing the severity of acute HZ associated pain in autoHCT recipients ≥18 YOA with confirmed HZ
- To evaluate VE in the reduction of HZ related and overall mortality in autoHCT recipients ≥18 YOA
- To evaluate VE in the reduction of HZ related and overall hospitalizations in autoHCT recipients ≥18 YOA

- To evaluate cell-mediated immunogenicity to the study vaccine in a sub-cohort of subjects

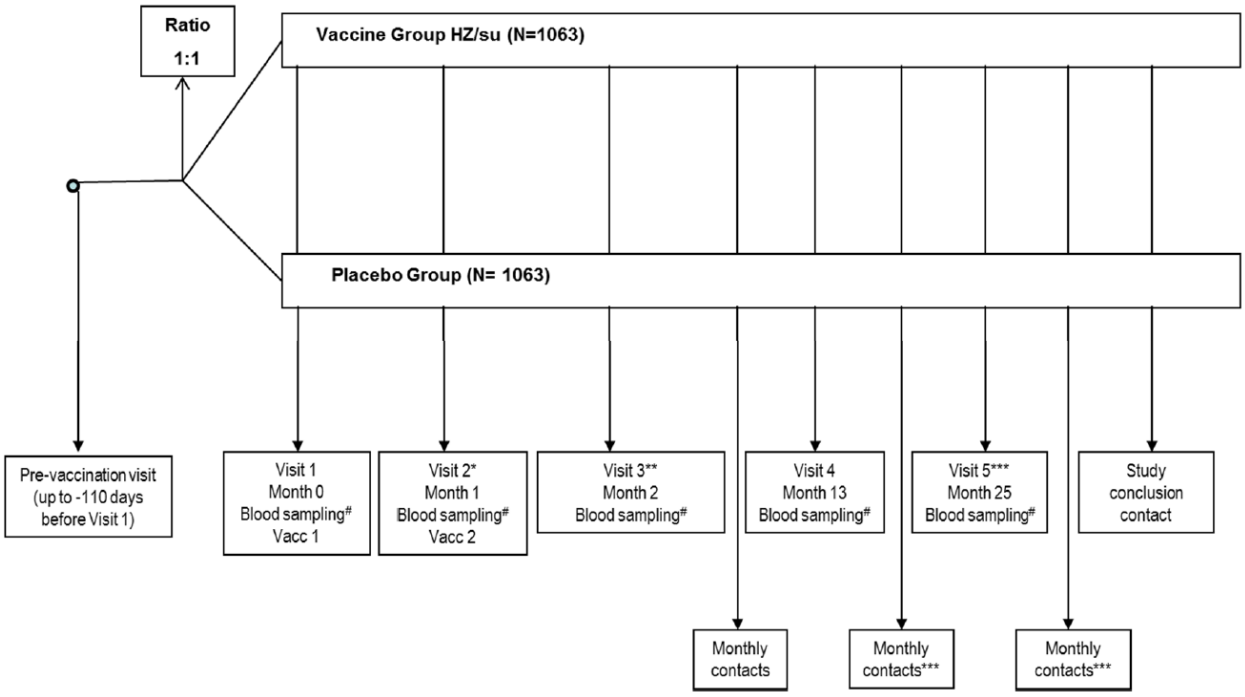
Reviewer comment: *Analyses of secondary and tertiary objectives were descriptive. Secondary endpoints and select tertiary endpoints are discussed below because they were proposed by the Applicant for inclusion in the PI or were determined to be potentially clinically pertinent.*

6.1.2 Design Overview

The study was a Phase 3 randomized, placebo-controlled, observer-blind, multicenter multi-national study with a planned enrollment of 2126 adult subjects ≥18 YOA who were status post autoHCT. Subjects were randomized 1:1 to receive two IM doses of HZ/su or placebo (lyophilized sucrose cake and saline solution) one month apart. The randomization algorithm used a minimization procedure to account for specific characteristics (see below).

A schematic of the study design (from IND 13879 Amendment 219) is presented below.

Figure 1. Overall Study Design, Zoster-002



Source: 125614/398.0, Zoster-002 CSR, Figure 1, p. 118
#Blood samples were collected from all subjects at Visit 1 and Visit 3, and additional blood samples were collected from sub-cohorts of subjects at all study visits to assess immune responses. If criteria for final triggered analysis were met before all subjects of the immunogenicity sub-cohorts reached Visit 5, then no blood sample for these subjects was taken anymore at Visit 5.
*The second dose of study vaccine/placebo was administered 1 to 2 months after the first dose.
**Visit 3 occurred approximately one month after the second vaccination.
***Each subject was to be followed at least until he/she completed Visit 4. Once conditions for final triggered analysis were met, all remaining monthly contacts after Visit 4, Visit 5, and monthly contacts after Visit 5 were not to take place.

Key elements of the study design included the following:

- A target enrollment of 2,126 eligible adult autoHCT recipients; assumptions for the sample size included an HZ incidence rate of 10%, 5%, 2.5% and 1.25% in years 1, 2, 3 and 4 after HCT, respectively; an HZ VE of 50%; and a non-evaluability rate (due to

dropouts and relapses) of 25% and 30% after the first and second year post-HCT, respectively.

- Treatment allocation at the site was performed using an internet-based randomization system. The randomization algorithm used a minimization procedure accounting for the following:
  - Age (18 – 49 YOA and ≥50 YOA)
  - Underlying disease (multiple myeloma or other diagnoses)
  - Post-transplant antineoplastic therapy (whether or not subjects were undergoing anti-neoplastic maintenance therapy with bortezomib at the time of first vaccination)
  - Anticipated duration of post-transplant antiviral therapy (up to and including 3 months or from more than 3 months up to and including 6 months)
  - Center
  - Gender

  A randomization algorithm was used to assign subjects to the immunogenicity sub-cohorts.
- Flexible timing of the second vaccination (from 1 – 2 months after first vaccination) to accommodate treatment schedules related to the subjects' underlying disease.
- A minimum study participation time of approximately 12 months after second vaccination (through Visit 4/Month 13). As the study was designed to be event-driven, participation time varied per subject.
- All subjects were scheduled for blood draws at Visits 1 and 3 to contribute to a correlate of protection assessment if the subject reported HZ or to be selected as a case control. Samples were collected at additional timepoints from subjects in the Humoral and CMI sub-cohorts.

6.1.3 Population

Key inclusion criteria

- Individuals ≥18 YOA at the time of study entry, who could provide written informed consent and who (in the opinion of the investigator) can and will comply with protocol requirements
- Has undergone or planned to undergo autoHCT within 50 – 70 days prior to first vaccination and without plans for additional HCT (tandem autoHCT recipients could participate following their final HCT)

Key exclusion criteria

- Previous vaccination against HZ or varicella within the 12 months prior to first study vaccination or occurrence of a varicella or HZ episode within 12 months prior to first study vaccination
- Prophylactic antiviral therapy (PAT) with activity against VZV expected to last more than 6 months after transplantation (i.e., subjects for whom PAT is expected to be given for 6 months or less following HCT may be enrolled)
- HIV infection by clinical history
- Pregnant or lactating female
- Administration or planned administration of a non-study vaccine between HCT and 30 days after the last dose of study product, except for licensed, non-replicating vaccines, which were allowed up to 8 days prior to dose 1 or 2, and/or at least 14 days after any dose of study product

Reviewer comment: *In general, consensus guidelines recommend that post-transplant administration of most vaccines begin approximately six months after transplantation (Tomblyn*

et al. 2009; Rubin et al. 2014). However, the dose schedule (doses 1 – 2 months apart, with the first dose 50 – 70 days following autoHCT), as well as the two-dose regimen evaluated in Zoster-002 were supported by the results of the Phase 1/2 study, Zoster-001.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study products were as follows:

Table 2. Vaccine and comparator composition/dose/lot number, Zoster-002

Treatment Name	Component Name*	Formulation	Presentation	Lot Numbers
HZ/su	VZV gE	50 µg gE per 0.5 mL of reconstituted vaccine	Lyophilized pellet in a monodose vial	DVZVA007A, DVZVA008A, DVZVA007B
HZ/su	$AS01_B$	MPL, QS21 and liposome (50 µg MPL and 50 µg QS21) per 0.5 mL of reconstituted vaccine	Liquid in a monodose vial	DA01A052A, DA01A055A, DA01A050A
Placebo	Lyophilized sucrose cake	(b) (4) sucrose per 0.5 mL of reconstituted placebo	Lyophilized pellet in a monodose vial	PVZVA003A, PVZVA005A
Placebo	Saline (NaCl) solution for reconstitution	(b) (4) NaCl solution (water for injection)	Liquid in a monodose vial	DD02A009A, DD02A011A

Source: Adapted from 125614/398.0 Zoster-002 CSR, Table 9, p. 137
VZV = varicella zoster virus; gE = recombinant purified glycoprotein E; $AS01_B$ = Adjuvant System $AS01_B$; NaCl = sodium chloride; MPL =3-O-desacyl monophosphoryl lipid A; QS21 = *Quillaja saponaria* Molina, fraction 21
* Components of the reconstituted study vaccine HZ/su and placebo, respectively.

6.1.5 Directions for Use

The vaccine or placebo was reconstituted and kept at room temperature prior to administration, which was to occur within 6 hours. The HZ/su vaccine or placebo were administered IM as a 0.5 mL dose to the deltoid region of the non-dominant arm. Following product administration, subjects were observed for at least 30 minutes with appropriate medical treatment available in the case of an anaphylactic reaction.

The second dose of HZ/su was to be administered within 30 to 60 days after the first dose.

Reviewer comment: *HZ/su was licensed as a two-dose series with the second dose administered 2 to 6 months after the first dose. In Zoster-002, the flexible scheduling for the second dose (i.e., within 1 – 2 months after the first dose) was pre-specified in order to accommodate treatment schedules for the subjects' underlying disease; the 0, 1 – 2 month schedule was supported by data from Zoster-001.*

6.1.6 Sites and Centers

The study was conducted at 167 centers in 28 countries in 4 regions. The majority of subjects (62.5%) were from Europe and South Africa.

Table 3. Number of subjects with centers by country and region, Zoster-002 (TVC)

Country	Region	Centers	HZ/sun (%) Total =922	Placebo n (%) Total =924
All countries	**Asia/Australia**	**All centers**	**187 (20.3)**	**193 (20.9)**
Australia	Asia/Australia	102119, 102120, 102121, 102122, 102123, 102526, 102527, 104963	46 (5.0)	48 (5.2)
Hong Kong	Asia/Australia	101741, 101742	9 (1.0)	6 (0.6)
Japan	Asia/Australia	100843, 100844, 100845, 100846, 100847, 100848, 100849, 100853, 100854, 105025, 208103	42 (4.6)	38 (4.1)
Korea, Republic of	Asia/Australia	100687, 100688, 100689, 100690, 100691, 100692 100694, 100695, 100731	66 (7.2)	67 (7.3)
Malaysia	Asia/Australia	104132, 104133	13 (1.4)	11 (1.2)
New Zealand	Asia/Australia	105687, 105689	2 (0.2)	3 (0.3)
Taiwan	Asia/Australia	105150, 105151, 105152, 105153	9 (1.0)	20 (2.2)
All countries	**Europe and South Africa**	**All centers**	**581 (63.0)**	**572 (61.9)**
Belgium	Europe and South Africa	101082, 101084, 101085, 101261 101277, 101481, 201247, 202252	28 (3.0)	27 (2.9)
Bulgaria	Europe and South Africa	107436	9 (1.0)	10 (1.1)
Czechia	Europe and South Africa	101109, 101110, 101111, 206170	36 (3.9)	30 (3.2)
Estonia	Europe and South Africa	100574	5 (0.5)	3 (0.3)
Finland	Europe and South Africa	101304, 101305, 101306	20 (2.2)	19 (2.1)
France	Europe and South Africa	101397, 101398, 101399, 101400, 101401, 101402 101403	45 (4.9)	41 (4.4)
Germany	Europe and South Africa	100382, 100386, 100388, 100390 100391, 100392, 100394, 100395, 100397, 100398, 100400, 100401 100402	50 (5.4)	54 (5.8)
Greece	Europe and South Africa	200275, 200276, 200278	10 (1.1)	7 (0.8)
Israel	Europe and South Africa	200268, 200273	20 (2.2)	19 (2.1)
Italy	Europe and South Africa	101042, 101043, 101045, 101068, 101072, 101073 101087, 101088	74 (8.0)	70 (7.6)
Netherlands	Europe and South Africa	200283	3 (0.3)	3 (0.3)
Poland	Europe and South Africa	101050, 205169, 207369	12 (1.3)	17 (1.8)
Romania	Europe and South Africa	200289	4 (0.4)	2 (0.2)

Country	Region	Centers	HZ/sun (%) Total =922	Placebo n (%) Total =924
Russian Federation	Europe and South Africa	201443, 201457, 201479, 201522, 201532, 215217 215218	18 (2.0)	17 (1.8)
South Africa	Europe and South Africa	100876, 101847, 102909	3 (0.3)	7 (0.8)
Spain	Europe and South Africa	100921, 100922, 100923, 100924, 100926, 100927 100929, 100930, 100932, 100934, 100935, 100936, 100937, 100938, 100939, 100940, 100941, 200796, 200797, 200798, 201409, 201448, 202295, 214005	168 (18.2)	171 (18.5)
Turkey	Europe and South Africa	104997, 104998, 215214, 215216	37 (4.0)	36 (3.9)
United Kingdom	Europe and South Africa	101507, 102001, 102012, 102018, 102023, 102024, 204625, 204626	39 (4.2)	39 (4.2)
All countries	**North America**	**All centers**	**149 (16.2)**	**153 (16.6)**
Canada	North America	100588, 100589, 100593, 100594, 100595, 101547	24 (2.6)	28 (3.0)
United States	North America	99279, 99280, 99281, 99282, 99283, 99296, 99298, 99300, 99303, 99318, 99319, 99394, 99438, 99443, 99444, 100064, 100304, 100389 100564, 100952, 102214	125 (13.6)	125 (13.5)
All countries	**South America**	**All centers**	**5 (0.5)**	**6 (0.6)**
Panama	South America	101056	5 (0.5)	6 (0.6)

Source: Adapted from BLA 125614/398.0, Zoster-002 CSR Table 6.3, pp. 1652 – 1655; and 125614/398.9, Responses to IR received April 22, 2021, Question 10, Table 1, p. 18

Reviewer comment: *The US was the second highest enrolling country. However, a large majority (86%) of subjects in the study came from outside of the US. Treatment for diseases in individuals receiving autoHCT can vary by country and may not reflect US standard of care. See reviewer comments in section 6.1.10 below. In addition, the epidemiology of HZ in non-varicella-controlled countries, may be different than in the US.*

6.1.7 Surveillance/Monitoring

Study oversight

An Independent Data Monitoring Committee, consisting of clinical experts (independent of the study protocol and external to the Applicant) and an independent statistician reviewed unblinded safety data on an ongoing basis and recommended whether to continue, modify or discontinue the trial.

Safety assessment – solicited AEs

Subjects were issued diary cards to record solicited symptoms daily from D0 through D6 following each vaccination, including the maximum symptom intensity, the end date, and any medical attention received for the event. The following local symptoms were solicited: injection

site (IS) pain, IS swelling and IS redness. The following general symptoms were solicited: fever, headache, fatigue, myalgia, gastrointestinal symptoms (including nausea, vomiting, diarrhea and/or abdominal pain), and shivering. Temperature was measured daily, preferably by the oral route and in the evening. If taken more than once a day, the highest daily temperature was recorded.

The maximum intensity of IS redness and swelling were measured by the subject and scored by the Applicant using the following grading scale: Grade 0: <20 mm diameter, Grade 1: ≥20 mm to ≤50 mm diameter, Grade 2: >50 mm to ≤100 mm diameter, Grade 3: >100 mm diameter. Fever was defined as temperature of ≥37.5°C/99.5°F by the oral route, and body temperature for the oral route was graded by the Applicant as follows: Grade 0: <37.5°C, Grade 1: ≥37.5°C - ≤38.5°C, Grade 2: >38.5°C - ≤39.5°C, Grade 3: >39.5°C.

Reviewer comment: *In Zoster-002, the Applicant's grading scale for fever differs from the scale that is used in the PI for the older adult population, where Grade 3 is defined as >39°C, and for other studies submitted in this sBLA. The FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Food and Drug Administration 2007), specifies a Grade 4 fever as >40°C (>104°F); The Applicant does not specify a Grade 4. Each of these temperature increments was evaluated by the reviewer.*

Non-ordinal events such as pain and solicited general symptoms were graded as follows: Grade 0 – none or normal, Grade 1 – mild, symptom easily tolerated, Grade 2 – moderate, interferes with normal activity, Grade 3 – severe, prevents normal activity.

All solicited local (IS) reactions were considered causally related to vaccination.

Safety assessment – unsolicited AEs
AEs were defined as per 21 CFR 312.32.

Unsolicited AEs were collected and recorded from Days 0 through 29 following each vaccination on a diary card. The card had space to record the maximum intensity of the AE, the start and end dates, and whether medical attention was sought for the AE. The grading scale was similar to the scale for non-ordinal solicited AEs. The subjects were asked a non-leading question at study contacts (e.g., "Have you felt different in any way since receiving the vaccine or since the previous visit?") to optimize collection of AEs.

The investigator determined the causal relationship of general/systemic AEs. The outcomes of any non-serious AE occurring within 30 days of vaccination and each SAE were recorded.

Reviewer comment: *The diary cards used for collection of solicited AEs and unsolicited AEs during the 30-day post-vaccination period were appropriately designed for the intended use.*

Safety assessment – medically attended adverse events (MAAEs)
For each AE/SAE occurring during the applicable reporting period, the subject was asked if he/she received medical attention and the information was entered on the electronic case report from (eCRF). Therefore, medically attended events were assessed during the unsolicited AE reporting period – the 30-day post-vaccination period.

Safety assessment – SAEs
AEs were defined as per 21 CFR 312.32.

The standard time period for reporting SAEs was from first vaccination to Visit 4/Month 13 (approximately 12 months following administration of last dose of study product), except for the following: SAEs related to the study vaccine were reported from first vaccination to the end of study, and fatal SAEs, and SAEs related to study participation or a concomitant medication/vaccination of the Applicant's were reported from pre-vaccination to the end of study.

Safety assessment – laboratory AEs and pregnancies
Abnormal laboratory findings or other assessments that were considered clinically significant by the investigator were recorded as AEs or SAEs, per protocol. Pregnancies were recorded from M0 until study end and followed for outcome.

Safety assessment – AEs of special interest (AESIs) and relapses
Due to the theoretical concern regarding the potentiation of immune-mediated AEs following non-alum adjuvanted vaccines, the occurrence or exacerbation of pIMDs (including autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology) were reported from first vaccination to Visit 4/Month 13 (approximately 12 months following administration of last dose of study product).

A list of pIMDs was included in the protocol. However, the investigator applied medical and scientific judgment in determining whether an AE was a pIMD.

Reviewer comment: *Any list or categorization of pIMDs is not exhaustive and is limited by the current understanding of such conditions. CBER accepted the Applicant's approach to allow the investigator (or the Applicant) to assign a potential immune mediated etiology to an event not on the list.*

Relapses or recurrences of the underlying malignancy or disease for which the HCT was undertaken, were recorded from Visit 1/M0 until study end.

Assessment – concomitant medications and vaccinations
The subject was queried about concomitant medications and vaccinations at each study visit, and there was space on the AE diary card for recording them. The following were recorded in the eCRF:

- All concomitant medications (except vitamins or dietary supplements, including medications taken in anticipation of a reaction to study product, administered any time between administration of each dose of study product and ending 30 days after administration of each dose of study product
- Any concomitant vaccination beginning 30 days before the first study dose until 30 days after last study dose
- Concomitant medication administered for the treatment of pIMDs from D0 until Month 13
- From D0 to study conclusion:
  - Any investigational medication or vaccine
  - Immunoglobulins or any blood product
  - Concomitant medication administered for the treatment of HZ or HZ-related complications
  - Concomitant medications or therapies administered for the treatment of relapse
  - Concomitant medication administered for the treatment of an SAE

- Any vaccine against varicella or HZ other than the study vaccine
- Antiviral therapy with activity against VZV

Reviewer comment*: CBER considered the assessments reasonable.*

Immunogenicity assessment

Blood samples were collected at pre-specified timepoints for a correlate of protection analysis and for analyses of the humoral and cellular immune response to vaccination as per the table below.

Table 4. Immunologic assessments and readouts, Zoster-002

Sample Type	Quantity (mL)	Visits	Group or Subset	Marker/Assay
Humoral assessment (serum)	8	1, 3	All subjects*	Anti-gE antibody/ELISA‡
Humoral assessment (serum)	8	1, 2, 3, 4, 5	Humoral immunogenicity subset	Anti-gE antibody/ELISA ‡
CMI assessment (PBMCs)	30	1, 2, 3, 4, 5	CMI sub-cohort†	gE challenge/Intracellular cytokine staining

Source: Adapted from 125614/398.0, Zoster-002 Protocol Amendment Administrative Change 1, Table 9, p. 74; Tables 10 and 12, p. 75; and Table 14, p. 76
PBMC = peripheral blood mononuclear cells
* These samples may have contributed to a correlate of protection analysis and to assess for VZV serostatus at baseline for subjects with suspected HZ
† The CMI sub-cohort was a sub-cohort of the humoral immunogenicity subset
‡ Cut-off for seropositivity was 97 mIU/mL

Reviewer comment*: According to the CMC reviewers, the anti-gE assay was validated for use as the primary immunologic read-out for the development program. However, it is widely acknowledged that adequate VZV-specific CMI is necessary for protection against HZ. There is no agreed upon vaccine-induced correlate of protection.*

Efficacy assessment- definitions

- Suspected HZ
  - A new rash characteristic of HZ (e.g., unilateral, dermatomal and accompanied by pain broadly defined to include allodynia, pruritus or other sensations), or a vesicular rash suggestive of VZV infection regardless of the distribution, and no alternative diagnosis; or
  - A clinical presentation (symptoms and/or signs) and specific laboratory findings (e.g., VZV-positive polymerase chain reaction (PCR), culture, immunohistochemical staining or other test performed in the course of medical evaluation, that strongly suggests VZV infection) suggestive of VZV infection in the absence of characteristic HZ or VZV rash
- Acute HZ pain – Defined as pain measured during the 4-week period following the onset of HZ
- PHN – Defined as the presence of HZ-associated 'worst' pain persisting or appearing more than 90 days after the onset of the HZ rash
- Severe "worst" HZ-associated pain – Defined as HZ-associated pain rated as 3 or greater on a 10-point pain scale on the "worst pain" question of the Zoster Brief Pain Inventory (ZBPI) questionnaire
- Disseminated HZ – Defined as ≥6 HZ lesions clearly outside the primary dermatome as per the investigator's judgment

Reviewer comment: *The protocol-specified definitions of HZ vasculitis, ophthalmic disease, neurologic disease, and visceral disease, HZ episode onset and end dates, and cessation of pain (to assess duration of HZ-associated pain) were acceptable.*

Efficacy assessment - questionnaires and scripts/cards

HZ-specific diary card – An HZ-specific diary card was distributed to each subject at Visit 1 to document the presence of the rash and/or pain, dates of onset, medications taken (including reason, route, dose, frequency and start and end dates). The card was reviewed at the first visit for suspected HZ.

Zoster Brief Pain Inventory (ZBPI) – The ZBPI is a version of the Brief Pain Inventory that is designed for individuals to characterize their experience with episodes of HZ. It assesses the occurrence, location and severity of pain (in four dimensions – worst, least, average, and now), receipt and impact of medications and therapies for the pain, and the impact of pain on daily function (e.g., walking, work, sleep) and emotional/mental status (e.g., mood, enjoyment of life). The ZBPI was used to measure HZ-associated pain (acute pain and PHN) during the study.

Reviewer comment: *The cards and questionnaires were reviewed and found acceptable for their intended purpose.*

Efficacy assessment – procedures for evaluation of suspected HZ

Subjects were educated about the signs and symptoms of HZ at study Visit 1 and were asked to complete HZ-specific diary cards and ZBPI questionnaires if they developed any signs or symptoms suggestive of HZ. If the subject suspected HZ, they were to visit the study site (if possible) or their attending physician to be evaluated. The following procedures were performed for cases suspected by the investigator to be HZ:

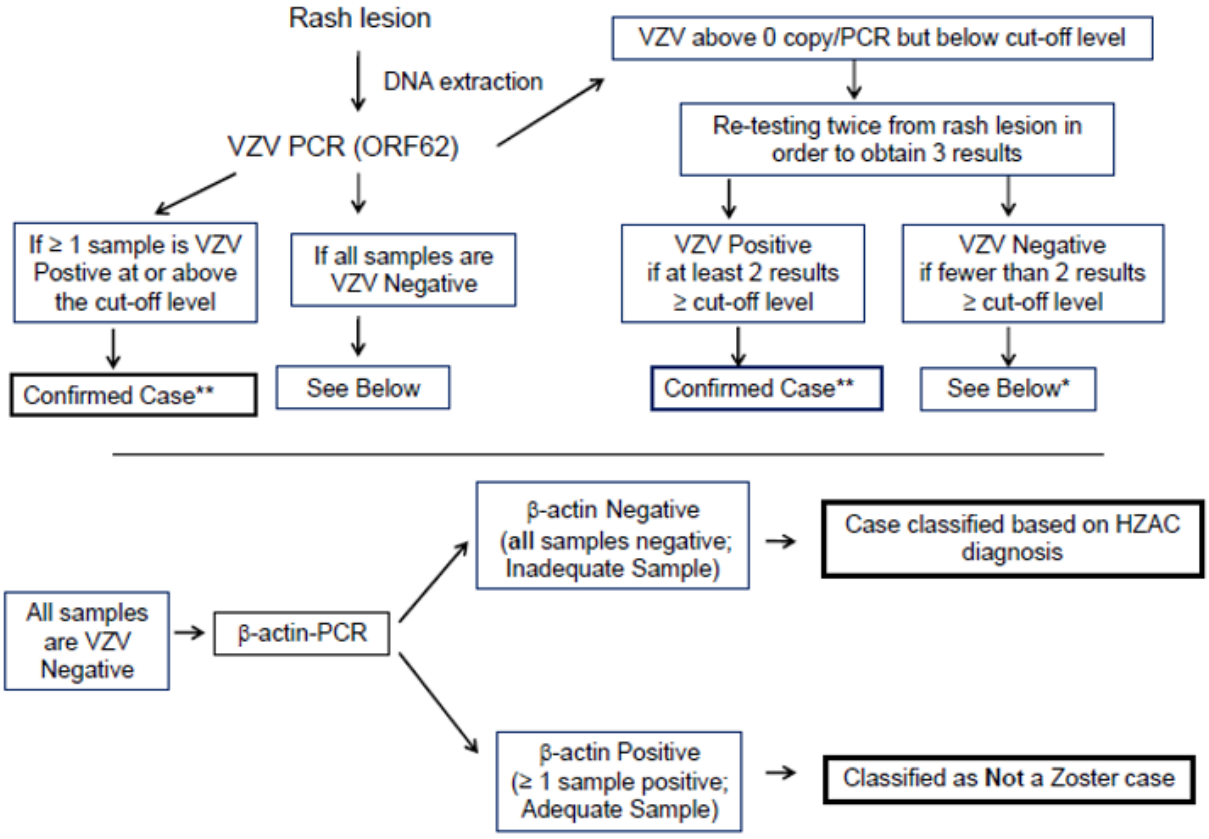
- Visit HZ-1/Day HZ-0
  - The investigator or delegate verified the completed HZ-specific diary card, collecting information about the episode (e.g., date of onset of pain and/or rash, location and nature of HZ lesions, HZ-related complications) and transcribed the information in the eCRF
  - Completed ZBPIs were verified (those completed prior to the visit and one completed at the visit to rate HZ-associated pain within the preceding 24 hours)
  - The rash was documented by digital photography and three replicate rash lesion samples collected (if available, if not and the rash progressed, the subject was to return for sample collection)
  - Any concomitant medications and medically attended visits related to the suspected HZ episode were recorded
  - The subject was provided with additional ZBPI and other questionnaires related to quality of life. Additional ZBPI questionnaires were to be completed from Day HZ-1 (the day after the first visit for suspected HZ) until Day HZ-28, and then weekly until a 28 day or 4-week pain-free period is documented.
- Additional HZ contacts were planned at Days HZ-7, HZ-14, HZ-21, HZ-28, HZ-56 and HZ-91 as well as monthly contacts if HZ-associated pain persisted beyond Day HZ-91. At each contact, information about the HZ episode (e.g., location and nature of HZ lesions, end date of the rash, HZ complications), any medically attended visits and concomitant medications/vaccinations were recorded, and the ZBPI was transcribed. Should subjects have ongoing HZ-associated pain at the time the study site was notified that the cut-off date for the final triggered analysis was reached, follow-up for the subject would continue for a minimum of 4 weeks after worst pain cessation.

As many of the procedures for evaluation (e.g., collection of rash lesion samples, photos of rash) would not have been applicable for cases of HZ without the characteristic rash, the protocol specified that initial assessment and ongoing care may be performed by an attending physician. In such cases, the study site was to contact the attending physician to collect relevant information to record on the eCRF.

Reviewer comment: *Results of the quality of life questionnaires, other than the ZBPI, are not discussed in this review.*

Efficacy assessment – classification of suspected cases of HZ
A suspected case of HZ was classified as a confirmed case of HZ or not a case of HZ according to the algorithm below.

Figure 2. Algorithm for HZ case definition by PCR, Zoster-002



Source: Adapted from 125614/398.0, Zoster-002 CSR, Figure 2, p. 147
VZV = Varicella Zoster Virus; PCR = real-time PCR; DNA = Deoxyribonucleic Acid; ORF = Open Reading Frame
*If the VZV PCR signal was above 0 copy/PCR but below the cut-off level of the assay, it was considered as "VZV borderline" and was re-tested twice in order to obtain three results per sample. The sample was considered "VZV positive" if at least 2 results out of the three obtained were ≥ the cut-off level of the assay and "VZV negative" if fewer than 2 results were ≥ the cut-off level of the assay. See then below 'All samples are VZV Negative.'
Note: The cut-off level of the VZV PCR assay is defined as the technical limit of detection (LOD) of the assay (LOD of 10 VZV DNA copies, i.e., lowest concentration that can be detected by PCR in at least 95% of the tests.

**Blood samples collected at Visit 1 prior to vaccination were used for testing of VZV serological status if all of the following three conditions applied:

- Subject was diagnosed with suspected HZ with typical VZV/HZ lesions, presented with disseminated rash from onset, and had VZV-positive PCR results, or VZV inconclusive PCR results, according to the algorithm above;
- Subject was born in 1980 or later, or was born before 1980 in a tropical region;
- No serological evidence of prior VZV infection was available at Visit 1.

In these subjects, a suspected HZ case with VZV positive or inconclusive PCR results according to the algorithm above was not considered a confirmed case of HZ if the subject was diagnosed with suspected HZ with typical VZV/HZ lesions and presented with a disseminated rash from onset, and the subject was VZV seronegative at baseline.

A VZV real-time PCR assay targeting the orf62 gene was used to detect the presence of VZV DNA in lesion samples. The technical limit of detection of the PCR assay was 10 VZV DNA copies. If all samples were negative, extracted DNA was assessed by PCR for the presence of β-actin (to determine the adequacy of the samples/validity of the rash lesion sampling procedure).

If a case could not be confirmed or excluded by PCR [i.e., if PCR results were inconclusive (VZV and β-actin negative) or not available], designation of a 'case' or 'not a case' of HZ was determined by a Herpes Zoster Adjudication Committee (HZAC), which adjudicated each case in a blinded manner.

The HZAC consisted of three physicians with expertise in infectious disease and hematology/oncology. Determination of 'a case' of HZ by the HZAC was required to be unanimous. If the case could not be confirmed or excluded by PCR and the final outcome of the HZAC for a case was 'not able to decide', the case was labeled 'no possible classification' and for analysis purposes, was considered as 'not HZ'.

Reviewer comment: *The 'not able to decide' classification by the HZAC was not pre-specified in the protocol.*

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint:

- Occurrence of confirmed HZ cases – the incidence of confirmed HZ cases from M0 until study end

  Success criterion: clinically meaningful overall HZ VE would be demonstrated if the lower bound (LB) of the 95% CI is above 0%.

  Reviewer comment: *A LB of VE of 0% is below what is usually considered acceptable for demonstration of efficacy, and LBs of VE of 10% and 25% were pre-specified in the two pivotal studies (Zoster-022 and Zoster-006, respectively) for licensure for HZ/su. CBER recommended a LB of 25% at the time of protocol review and the Applicant agreed to revise the protocol to power the study for a LB of 25% but decided to retain the same success criterion. CBER did not object to this approach.*

Secondary endpoints:

- Duration of 'worst' HZ-associated pain – Duration of HZ-associated pain rated as 3 or greater on the 'worst pain' ZBPI question, following a confirmed HZ rash during the entire pain reporting period
- Occurrence of confirmed HZ-associated complications – Incidence of confirmed HZ complications following the onset of HZ from M0 until study end
- Occurrence of PHN – Incidence of PHN from M0 until study end

- Antigen-specific Ab concentrations in a sub-cohort of subjects – Anti-gE Ab concentrations as determined by enzyme-linked immunosorbent assay (ELISA) in a sub-cohort of subjects at Months 0, 1, 2, 13 and 25
- Occurrence and intensity of solicited local symptoms and occurrence, intensity and relationship to vaccination of solicited general symptoms in all subjects within 7 days after each vaccination
- Occurrence, intensity and relationship to vaccination of unsolicited AE during the 30 days after each vaccination
- Occurrence and relationship to vaccination of all SAEs from M0 to M13 in all subjects
- Occurrence of SAEs
  - Occurrence and relationship of all SAEs from M0 – M13 in all subjects
  - Occurrence of SAEs related to study products from M0 until study end in all subjects
  - Occurrence of SAEs related to study participation or to a concurrent medication/vaccine of the Applicant's or any fatal SAE from a pre-vaccination visit until study end in all subjects
- Occurrence of AEs of special interest
  - Occurrence and relationship to vaccination of any pIMDs from M0 – M13 in all subjects
  - Occurrence of relapse cases from M0 until study end in all subjects

Select tertiary endpoints

- Incidence of confirmed HZ cases in subjects at least one year post-HCT
- Incidence of PHN from M0 until study end in subjects with confirmed HZ
- Acute HZ severity as measured by the ZBPI during a 4-week period following the onset of confirmed HZ (in subjects with confirmed HZ)
- Occurrence of overall (in all subjects) mortality, HZ-related mortality, overall hospitalizations, HZ/related hospitalizations from M0 until study end
- CMI in terms of frequencies of antigen-specific CD4 T-cells in a sub-cohort of subjects
- Anti-gE Ab concentrations as determined by ELISA at M0 and M2 in all subjects with confirmed HZ compared to matched controls

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size assumptions

The sample size was selected to provide the required number of cases within a follow up time of 3150 person-years and accounted for a 25% non-evaluable rate for the first year and an additional 30% non-evaluable rate for the following years assuming an HZ incidence rate of 10%, 5%, 2.5% and 1.25% per year in years 1, 2, 3, and 4, respectively, following HCT.

Missing data

For a given subject and a given efficacy measurement, missing or non-evaluable measurements were not imputed for the primary analysis. For the analysis of solicited symptoms, only subjects/doses with documented safety data were included in the analysis. For the analysis of unsolicited AEs and concomitant medications, subjects who did not report an event or medication were considered subjects without an event or medication.

Planned analysis

No interim analyses were planned.

One final triggered analysis was planned when both of the following occurred:

- when 125 cases of HZ were accrued in the modified total vaccinated cohort (mTVC)
- when all subjects had completed Visit 4

Reviewer comment: *Vaccine efficacy may be more robust within the months after vaccination and may wane over time. The requirement for all subjects to complete Visit 4 prior to the final triggered analysis ensured that efficacy would be evaluated up to a year post-vaccination. The one-year follow-up was also consistent with CBER's request for one-year of safety monitoring of non-aluminum-based adjuvants.*

Analysis of efficacy

The primary population for the analysis of efficacy was the mTVC. The primary analysis for VE against HZ considered the exact inference on the relative risk conditionally to the total number of HZ cases observed and time at risk. The time at risk was calculated (for the mTVC) from 30 days following the last second vaccination to HZ onset. Subjects with relapse of the malignancy or disease for which the autoHCT was administered were censored from the mTVC from the date that they started therapy for relapse. An additional analysis was planned to evaluate VE in the prevention of HZ when all subjects had reached one-year post-HCT. The HZ incidence rate was determined using the first confirmed HZ case (event) observed in a subject if several HZ cases occurred in the same subject.

The analysis of the reduction in overall PHN risk was similar to that of HZ risk using the exact inference on the relative risk conditionally to the total number of PHN cases observed and time at risk.

Reviewer comment: *Please see the statistical review for additional details about the analyses of select secondary endpoints. In his review, the statistical reviewer did not comment on the methodology of the analyses of all secondary and tertiary endpoints; however, the results of these analyses that may be of interest to stakeholders are included in this clinical review.*

Analysis of immunogenicity

The primary population for the analysis of immunogenicity was the according to protocol (ATP) cohort for immunogenicity, which included all evaluable subjects (i.e., those meeting eligibility criteria, who complied with protocol and who did not meet protocol-defined elimination criteria) for whom data for the immunogenicity endpoint was available. The term "Adapted ATP cohort" for Immunogenicity is used to signify the appropriate time cohort was used.

For the purposes of humoral immunogenicity analyses:

- A seronegative subject = subjects with an Ab concentration < the cut off level (97 mIU/mL)
- A seropositive subject = subject whose Ab concentration is ≥ the cut off level

gE-specific humoral immune vaccine response is defined:

- For subjects seropositive at baseline – a 4-fold increase in the anti-gE Ab concentration at the endpoint compared to the pre-vaccination anti-gE Ab concentration
- For subjects seronegative at baseline – a 4-fold increase in the anti-gE Ab concentration at the endpoint compared to the anti-gE cut off value for seropositivity

Reviewer comment: *Although not pre-defined in the protocol, the humoral vaccine response rate (VRR) was assessed as the percentage of subjects demonstrating a humoral vaccine response.*

Analysis of safety
The primary population for the analysis of safety was the total vaccinated cohort (TVC). Safety analysis was descriptive and was provided overall and by time of occurrence relative to the last vaccination as pre-specified in the study objectives.

Reviewer comment: *Please see the statistical review for further details about the statistical methods used for the immunogenicity and safety analyses.*

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All subjects enrolled belonged to the total enrolled cohort. The total vaccinated cohort (TVC) was the primary population for the analysis of safety and included all vaccinated subjects with respect to the vaccine actually administered.

The mTVC was the primary population for the analysis of efficacy. The mTVC excluded subjects in the TVC analysis who:

- did not receive a second vaccination or
- were cross treated or
- developed a confirmed case of HZ prior to one month after the second vaccination

Reviewer comment: *In the review of the original BLA and IND studies supporting it, CBER agreed that the mTVC as defined was an appropriate population for the primary analysis of HZ VE. A protocol-specified analysis of efficacy on the TVC was also planned as a sensitivity analysis.*

The according to protocol cohort for immunogenicity evaluations included all evaluable subjects (i.e., those meeting all eligibility criteria, who complied with the protocol without elimination criteria during the study) for whom data for immunogenicity endpoint measurements were available.

Demographics

The summary of demographic characteristics of the TVC is below.

Table 5. Summary of demographic characteristics, Zoster-002 (TVC)

Characteristic	HZ/su N=922 n (%)	Placebo N=924 n (%)	Total N=1846 n (%)
Age (years) at dose 1			
Mean (SD)	54.8 (11.7)	55.1 (11.4)	55.0 (11.6)
Median (min, max)	57.0 (18, 78)	58.0 (18,75)	57.0 (18, 78)
Age stratum			
18 – 49 YOA	230 (24.9)	229 (24.8)	459 (24.9)
≥50 YOA	692 (75.1)	695 (75.2)	1387 (75.1)

Characteristic	HZ/su N=922 n (%)	Placebo N=924 n (%)	Total N=1846 n (%)
Gender			
Female	342 (37.1)	346 (37.4)	688 (37.3)
Male	580 (62.9)	578 (62.6)	1158 (62.7)
Ethnicity			
American Hispanic or Latino	26 (2.8)	27 (2.9)	53 (2.9)
Not American Hispanic or Latino	896 (97.2)	897 (97.1)	1793 (97.1)
Geographic Ancestry			
African Heritage / African American	15 (1.6)	25 (2.7)	40 (2.2)
American Indian or Alaskan Native	2 (0.2)	0 (0.0)	2 (0.1)
Asian - Central/South Asian Heritage	6 (0.7)	5 (0.5)	11 (0.6)
Asian - East Asian Heritage	83 (9.0)	91 (9.8)	174 (9.4)
Asian - Japanese Heritage	43 (4.7)	38 (4.1)	81 (4.4)
Asian - South East Asian Heritage	18 (2.0)	16 (1.7)	34 (1.8)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White - Arabic / North African Heritage	9 (1.0)	12 (1.3)	21 (1.1)
White - Caucasian / European Heritage	715 (77.5)	712 (77.1)	1427 (77.3)
Other	31 (3.4)	25 (2.7)	56 (3.0)

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 29, p. 216
TVC = total vaccinated cohort; N = total number of subjects; n/% = number / percentage of subjects in a given category; SD = standard deviation

Most subjects were male (62.7%), non-American Hispanic or Latino (97.1%) and White of Caucasian/European heritage (77.3%).

Reviewer comment: *The median age and proportions of subjects by gender, race and ethnicity were comparable between treatment groups for the TVC. The Applicant provided an analysis of demographics and other characteristics of subjects enrolled in Zoster-002 compared to population-based demographics of subjects in the US receiving autoHCTs (125614/398.5). Of 13,376 autoHCTs performed in the US in 2018 (representing >85% of autoHCTs in the US), race information, collected for 51% of subjects, showed that 69.5% were White, 20% were African American, and 10.5% were Hispanic (D'Souza et al. 2020). Although there was a notable increase in the number of African Americans and Hispanics receiving autoHCT for multiple myeloma between 2010 and 2018, these race and ethnic groups are still underrepresented in the total Zoster-002 study population compared to the population receiving HCTs in the US. Based on another analysis of an insurance claims database in the US, of 969 patients who received an autoHCT, 37.3% were female and 15.5% were 18 – 40 YOA (Broder et al. 2017). The proportion of subjects 18 – 40 YOA enrolled in Zoster-002 was 12.6%. Although this represents a subset of autoHCTs performed in the US, demographics by gender and age were similar in Zoster-002 to those assessed in the claims analysis.*

The Applicant provided a summary of demographic characteristics in the mTVC, the population used for the efficacy analysis. There were no clinically significant differences in demographic characteristics between the TVC and the mTVC.

Of note, the Applicant used "American Hispanic/Latino" in Zoster-002, Zoster-039, and the ISS, but did not use this terminology in all studies (for example, Zoster-041). It appears that subjects enrolled in Spain were not included as "American Hispanic/Latino."

The Applicant also provided demographic characteristic summaries by age subgroups,18 – 49 and ≥50 years of age. Four hundred and fifty-nine subjects (24.9%)18 – 49 YOA were enrolled

in the TVC, 230 (24.9%) in the HZ/su group and 229 (24.8%) in the placebo group. Based on the information in the datasets, the number of subjects in the TVC in the younger age stratum approximately by decade were 86 subjects 18 – 29 YOA (48 in the HZ/su group, 38 in the placebo group), 126 subjects 30 – 39 YOA (62 in the HZ/su group, 64 in the placebo group), and 247 subjects 40 – 49 YOA (120 in the HZ/su group, 127 in the placebo group).

Reviewer comment: *Within each age strata,18 – 49 and ≥50 YOA, demographic characteristics were generally similar between treatment groups. Subjects as young as age 18 were enrolled into both treatment groups.*

Medical/Behavioral Characterization of the Enrolled Population

The summary of subjects' underlying disease leading to autoHCT is presented below.

Table 6. Summary of subjects' underlying disease, Zoster-002 (TVC)

Characteristics	Parameters or Categories	HZ/su N=922 n (%)	Placebo N=924 n (%)	Total N=1846 n (%)
Underlying disease	Multiple Myeloma	490 (53.1)	493 (53.4)	983 (53.3)
	All other diagnoses	432 (46.8)	431 (46.6)	863 (46.7)
Select detailed underlying diseases	Non-Hodgkin B cell lymphoma	257 (27.9)	273 (29.5)	530 (28.7)
	Hodgkin lymphoma	82 (8.9)	66 (7.1)	148 (8.0)
	Non-Hodgkin T cell lymphoma	48 (5.2)	45 (4.9)	93 (10.1)
	Acute myeloid leukemia	21 (2.3)	20 (2.2)	41 (2.2)

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 6.24, p. 1694; and 125614/398.9, Responses to IR received April 22, 2021, Question 11, Table 1, p. 19
TVC = total vaccinated cohort; N = total number of subjects; n/% = number / percentage of subjects in a given category

Reviewer comment: *In general, underlying diseases were balanced between vaccination groups; although there were slightly more subjects in the HZ/su group with Hodgkin lymphoma compared to the placebo group. Approximately 67% of autoHCTs performed in the US in 2018 were for multiple myeloma (MM) and related plasma cell disorders (D'Souza et al. 2020). Subjects enrolled in Zoster-002 from the US reflected this distribution (66% with MM); however, MM is underrepresented in the entire Zoster-002 TVC compared to the US population receiving autoHCTs.*

The Applicant presented demographics by underlying disease [multiple myeloma (MM) and 'all other diagnoses']. Subjects with MM were older than those with 'all other diagnoses' [Mean (SD, minimum – maximum) 58.8 years (7.8 years, 30 – 75 years) with MM, 50.5 years (13.4 years, 18 – 78 years) with 'all other diagnoses']. There were more subjects of 'African Heritage/African Americans' enrolled with MM compared to 'all other diagnoses' (33 with MM, 7 with 'all other diagnoses'), though overall numbers of subjects of 'African Heritage/African Americans' are low in both groups.

The protocol specified study vaccine was to be administered 50 – 70 days post-autoHCT. The median time between transplant and first vaccination in the TVC was 61.0 days, with a minimum of 32 days and a maximum of 92 days. A CBER analysis determined that dose 1 of HZ/su was administered out of the specified window following auto-HCT to 16 subjects (1.7%) in the HZ/su group (15 subjects <50 days and 1 subject > 70 days post-autoHCT) and 17 subjects (1.8%) in the placebo group (11 subjects <50 days and 6 subjects > 70 days post-autoHCT).

Subjects with six months or less anticipated duration of prophylactic antiviral therapy (PAT) for HZ were eligible for enrollment. In the mTVC, 979 subjects (56.9%) were anticipated to receive 0 – 3 months of PAT and 742 subjects (43.1%) were anticipated to receive more than 3 up to 6 months of PAT. The Applicant provided an analysis of VE by actual duration of PAT in the Comprehensive Summary of Efficacy, which indicated that 51.1%, 28.4%, and 20.5% of the mTVC did not receive PAT, received PAT for 1 – 60 days, and received PAT for >60 days, respectively. For subjects who received PAT, the median (minimum – maximum) duration of PAT was 57 days (1 – 1,121 days) in the HZ/su group and 53 days (1 – 1,442 days) in the placebo group.

Reviewer comment: *AutoHCT patients in the US are generally recommended to receive PAT for one-year post-transplantation (Tomblyn et al. 2009); this study evaluated HZ/su VE in subjects receiving shorter duration PAT than is typically prescribed in the US. Actual duration of PAT was similar between the two treatment groups.*

In the Comprehensive Summary of Efficacy, the Applicant provided a summary of the immunosuppressive treatments subjects in the mTVC received (see below).

Table 7. Summary of immunosuppressive treatment received by subjects in the HZ/su group from 30 days prior to HCT up to 30 days after Dose 2, Zoster-002 (mTVC)

Immunosuppressive Treatment	HZ/su N=870 n (%)	Placebo N=851 n (%)
Anthracyclines	7 (0.8)	1 (0.1)
Anti CD20	35 (4.0)	37 (4.3)
Anti-mitotic agents (including antimicrotubule agents)	8 (0.9)	1 (0.1)
Anti-TNF non-monoclonal antibodies	128 (14.7)	126 (14.8)
Calcineurin inhibitors	3 (0.3)	1 (0.1)
Chemotherapy/antineoplastic agents, not specified	1 (0.1)	2 (0.2)
Folic acid analogues	6 (0.7)	5 (0.6)
Guanine synthesis inhibitors	1 (0.1)	1 (0.1)
Highly immunosuppressive monoclonal Ab	0 (0)	1 (0.1)
Low immunosuppressive monoclonal Ab	2 (0.2)	0 (0)
Nitrogen and mustard analogues	838 (96.3)	827 (97.2)
Nitrosoureas	278 (32.0)	276 (32.4)
Other alkylating agents	96 (11.0)	96 (11.3)
Other cytotoxic antibiotics	1 (0.1)	1 (0.1)
Other targeted therapies	2 (0.2)	1 (0.1)
PK inhibitors	0 (0)	2 (0.2)
Platinium compound	12 (1.4)	13 (1.5)
Polyclonals	1 (0.1)	1 (0.1)
Proteasome inhibitors	82 (9.4)	79 (9.3)
Purine analogues	1 (0.1)	1 (0.1)
Pyrimidine analogues	288 (33.1)	278 (32.7)
Radio-immunoconjugates	1 (0.1)	2 (0.2)
Topoisomerase inhibitors	333 (38.3)	325 (38.2)
Total body irradiation	16 (1.8)	13 (1.5)

Source: Adapted from 125614/398.0, Comprehensive Summary of Efficacy, Appendix Table 27, pp. 136 - 137
mTVC = modified total vaccinated cohort; N = total number of subjects; n/% = number / percentage of subjects receiving any immunosuppressive ingredient sub-class at least 1 day within the specified period; TNF = tumor necrosis factor; PK = protein kinase

Reviewer comment: *There were no clinically significant differences between vaccination groups based on immunosuppressive therapy used up to 30 days after dose 2. Proteosome*

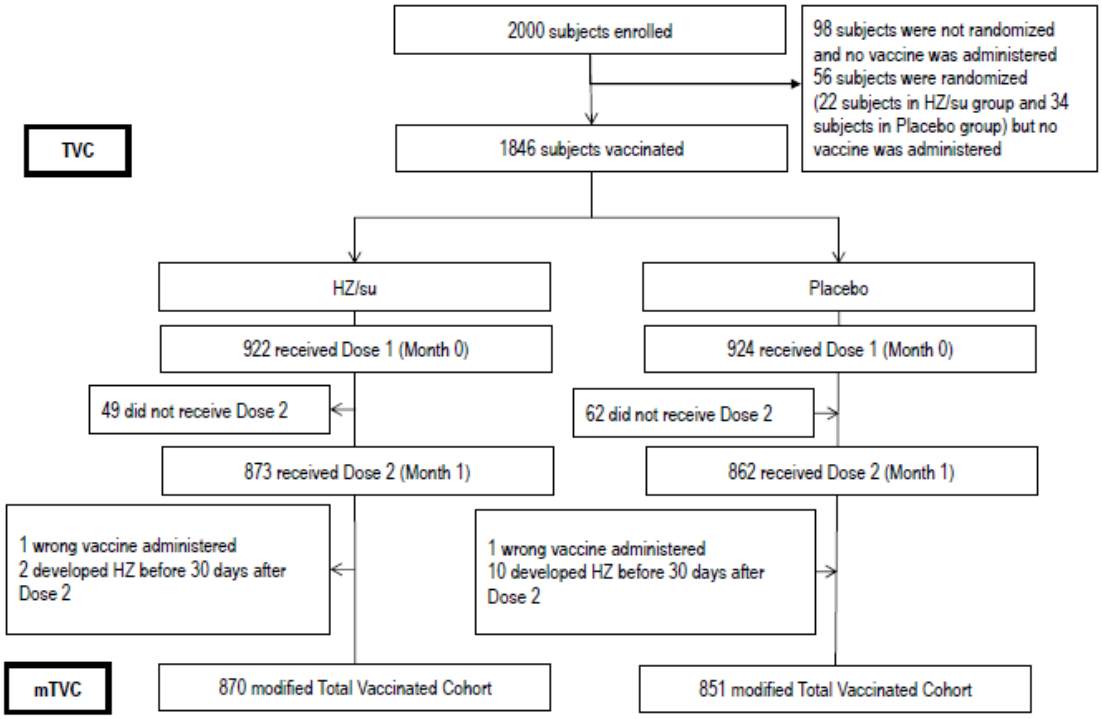
inhibitors, such as bortezomib, are used to treat MM and are associated with a higher incidence of HZ. Only 9.4% of subjects received a proteasome inhibitor, such as bortezomib, through 30 days post-dose 2 and 13.9% received this medication class through the end of the study follow-up for efficacy (not shown), with a similar proportion of subjects receiving proteasome inhibitors in each treatment group. In the Applicant's presentation of immunosuppressive therapies used in the US and other countries (125614/398.5), there was variability between regions in proportion of subjects receiving some therapies in Zoster-002. This may reflect differences in therapies used between regions and differences in underlying diseases (see above).

Subject Disposition

Of the 2,000 subjects in the total enrolled cohort, 1846 were vaccinated and comprised the TVC. One hundred fifty-four subjects did not receive vaccine because they no longer met the eligibility requirements on Day 1/Visit 1.

The figure below shows the number of subjects included in the total enrolled cohort, the TVC, and mTVC with reasons for exclusion.

Figure 3. Subject disposition, Zoster-002 (mTVC)



Source: 125614/398.0, Zoster-002 CSR, Figure 3, page 209
mTVC = modified total vaccinated cohort

Overall, 1721 subjects (93.2% of the TVC) were included in the mTVC for the analysis of efficacy: 870 subjects (94.4%) and 851 subjects (92.1%) from the TVC of the HZ/su and placebo groups, respectively. Of the excluded subjects, the majority were excluded due to not receiving two doses (See the Exposure section below).

Reviewer comment: *The proportion of subjects in the TVC that were included in the mTVC for the analysis of efficacy was comparable between treatment groups.*

Exposure

A total of 111 (6.0%) subjects out of 1846 in the TVC did not receive the second vaccination; 49 (5.3%) in the HZ/su group and 62 (6.7%) in the placebo group.

Table 8. Number and percentage of subjects who received one or both study vaccine doses, Zoster-002 (TVC)

Total Doses Received	HZ/su N=922 n (%)	Placebo N=924 n (%)	Total N=1846 n (%)
1	49 (5.3)	62 (6.7)	111 (6.0)
2	873 (94.7)	862 (93.3)	1735 (94.0)
Any	922 (100)	924 (100)	1846 (100)

Source: 125614/398.0, Zoster-002 CSR, Table 10.1, page 2293
TVC = total vaccinated cohort; N = number of subjects in each group or in total; n/% = number/percentage of subjects receiving the specified total number of doses; Any = number and percentage of subjects receiving at least one dose

Reviewer comment: *A high proportion of subjects in each treatment group received both doses. Exposure by age stratum (18 – 49 YOA and ≥50 YOA) was reviewed. Similar proportions of subjects in each treatment group and in each age stratum received both doses (92.9 – 95.2%).*

The reasons that subjects in the TVC did not receive a second vaccination are displayed below by vaccination group.

Table 9. Number and percentage of subjects withdrawn from vaccination (did not receive dose 2) by reason for withdrawal, Zoster-002 (TVC)

	HZ/su N=922 n (%)	Placebo N=924 n (%)
Did not receive dose 2	49 (5.3)	62 (6.7)
Reason dose 2 not administered		
SAE	6 (0.7)	6 (0.6)
Non-serious adverse event	7 (0.8)	5 (0.5)
Suspected HZ Episode	8 (0.9)	10 (1.1)
Other	2 (0.2)	2 (0.2)
Visit not done	26 (2.8)	39 (4.2)
Visit not done reason		
SAE or pIMD	7 (0.8)	8 (0.9)
Non-serious AE	4 (0.4)	10 (1.1)
Consent withdrawn	6 (0.7)	9 (1.0)
Lost to follow-up	1 (0.1)	0
Protocol violation	1 (0.1)	3 (0.3)
Suspected HZ Episode	3 (0.3)	6 (0.6)
Other	4 (0.4)	3 (0.3)

Source: Adapted from 125614/398.9, Responses to IR received April 22, 2021, Question 7, Table 1, p. 14
TVC = total vaccinated cohort; N = number of subjects in each group or in total; n/% = number / percentage of subjects the subjects that were withdrawn from vaccination for the specified reason; SAE = serious adverse event; pIMD = potentially immune-mediated disease

Reviewer comment: *The Applicant presented reasons for vaccine withdrawal separate from reasons no vaccination visit was completed at M1 (submitted in response to an IR in 125614/398.9). More subjects in the placebo group did not receive the second vaccination because more subjects in the placebo group reported a non-serious AE or withdrew consent*

and so did not complete Visit 2. The proportion of subjects in the TVC withdrawn from vaccination because of a serious or non-serious AE was similar between vaccination groups. Please see the discussion of AEs leading to withdrawal (including withdrawal from vaccination) in section 6.1.12.7.

Protocol deviations

Protocol deviations not leading to elimination from analyses (section 6.3.2 of the CSR) were also reviewed. These deviations involved informed consent forms, late reporting of safety events, errors in biospecimen collection, vaccine administration, randomization timing, unblinded staff performing evaluations, and study assessments performed or not performed per protocol.

Reviewer comment: *The Applicant's documentation of the deviations not leading to exclusion from analyses as well as corrective actions taken were reviewed and found to be acceptable.*

Disposition

Of the 1846 subjects included in the TVC, a total of 480 subjects (228 and 252 in the HZ/su group and placebo group, respectively) did not complete the study (November 4, 2016). 244 subjects (13.2% of TVC) were withdrawn before Visit 4 (Month 13); 135 subjects (7.3%) were withdrawn between Visit 4 and Visit 5 (Month 25); and 101 subjects (5.5%) were withdrawn after Visit 5. Total withdrawals were similar between treatment groups at each time point.

The number of subjects withdrawn and reasons for withdrawal at each time point are presented below. Reasons for withdrawal after Visit 5 (Month 25) were not required to be documented per protocol. Out of 101 subjects withdrawn after Visit 5, 49 subjects died (26 subjects in the HZ/su group and 23 subjects in the placebo group).

Table 10. Number of subjects vaccinated and withdrawn until Visit 4, between Visit 4 and 5, and after Visit 5, but prior to the cut-off date for final analysis (November 4, 2016) with reason for withdrawal, Zoster-002 (TVC)

Disposition	HZ/su n (%)	Placebo n (%)	Total n (%)
Number of subjects vaccinated	**922 (100)**	**924 (100)**	**1846 (100)**
Number of subjects completed	**694 (75.3)**	**672 (72.7)**	**1366 (74.0)**
Number of subjects withdrawn until Visit 4	**115 (12.5)**	**129 (14.0)**	**244 (13.2)**
Reasons for withdrawal:			
Serious Adverse Event or pIMD	65 (7.0)	67 (7.3)	132 (7.2)
Non-Serious Adverse Event	14 (1.5)	14 (1.5)	28 (1.5)
Protocol violation	3 (0.3)	1 (0.1)	4 (0.2)
Consent withdrawal (not due to an adverse event)	23 (2.5)	30 (3.2)	53 (2.9)
Migrated/moved from study area	2 (0.2)	4 (0.4)	6 (0.3)
Lost to follow-up (subjects with incomplete vaccination course)	2 (0.2)	1 (0.1)	3 (0.2)
Lost to follow-up (subjects with complete vaccination course)	2 (0.2)	5 (0.5)	7 (0.4)
Suspected HZ Episode	1 (0.1)	3 (0.3)	4 (0.2)
Others	3 (0.3)	4 (0.4)	7 (0.4)

Disposition	HZ/su n (%)	Placebo n (%)	Total n (%)
Number of subjects withdrawn between Visit 4 and 5	**65 (7.0)**	**70 (7.6)**	**135 (7.3)**
Reasons for withdrawal:			
Serious Adverse Event	35 (3.8)	38 (4.1)	73 (4.0)
Non-Serious Adverse Event	8 (0.9)	4 (0.4)	12 (0.7)
Protocol violation	0 (0.0)	2 (0.2)	2 (0.1)
Consent withdrawal (not due to an adverse event)	7 (0.8)	8 (0.9)	15 (0.8)
Migrated/moved from study area	4 (0.4)	2 (0.2)	6 (0.3)
Lost to follow-up (subjects with incomplete vaccination course)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up (subjects with complete vaccination course)	5 (0.5)	9 (1.0)	14 (0.8)
Suspected HZ Episode	0 (0.0)	0 (0.0)	0 (0.0)
Others	6 (0.7)	7 (0.8)	13 (0.7)
Number of subjects withdrawn after Visit 5	**48 (5.2)**	**53 (5.7)**	**101 (5.5)**

Source: Adapted from 125614/398.0, Zoster-002 CSR, Tables 25, 26, and 27, pp. 205 – 206
TVC = total vaccinated cohort; n/% = number / percent of subjects with disposition or reason

Reviewer comment: *The withdrawal rate (13% in the year post-last vaccination) and predominant reason for withdrawal being an AE/SAE is not unexpected in this post-autoHCT population and is less than the Applicant anticipated (25%). The numbers of subjects withdrawn and reasons were similar between groups.*

6.1.11 Efficacy Analyses

The final analysis of HZ VE was performed on the mTVC. Efficacy analyses supportive to the primary analysis of the mTVC were also performed on the TVC. Except for the analyses of the primary endpoint, all the other analyses (of secondary and tertiary endpoints including by subgroup analyses) were exploratory. The VE analyses on the TVC was consistent with the analyses on the mTVC and are not discussed below.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint of the study was confirmed first or only episode of HZ during the study. Confirmed HZ episodes that occurred after start of treatment for relapse of the underlying disease were not considered in this analysis.

Of the 264 suspected HZ episodes (74 in the HZ/su group and 190 in the placebo group), 54 (73.0%) in the HZ/su group and 148 (77.9%) in the placebo group were confirmed HZ episodes. In the HZ/su group, of the 54 confirmed HZ episodes, 45 (83.3%) were confirmed by PCR and 9 (16.7%) by HZAC. In the placebo group, of the 148 confirmed HZ episodes, 122 (82.4%) were confirmed by PCR and 26 (17.6%) by HZAC.

Reviewer comment: *A majority of HZ episodes in both treatment groups were confirmed by PCR.*

There were no subjects in the HZ/su group and three subjects in the placebo group with more than one confirmed HZ episode (two confirmed HZ episodes for each of the three subjects in the placebo group). Fifteen subjects with confirmed HZ (5 in the HZ/su group and 10 in the placebo group) reported the HZ episode occurring after starting treatment for a relapse.

After eliminating HZ episodes that occurred after the start of treatment for relapse and second HZ episodes, of the 184 subjects with confirmed HZ episodes considered in the analysis, 49 were in the HZ/su group and 135 were in the placebo group after a median follow-up time of approximately 21 months (approximately 22 months in the HZ/su group and 20 months in the placebo group). The overall incidence of HZ per 1000 PY was 30.0 in the HZ/su group and 94.3 in the placebo group, for an overall VE against HZ in this population of 68.2% (95% CI: 55.6, 77.5%). The primary objective of the study was met since the LB of the 95% CI was above 0%.

Table 11. Vaccine efficacy: First or only episode of HZ during the entire study period using Poisson method, Zoster-002 (mTVC)

Type	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LB 95% CI	VE UB 95% CI
Overall	870	49	1633.1	30.0	851	135	1431.9	94.3	68.2	55.6	77.5

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 31, p. 220
mTVC = modified total vaccinated cohort (subjects who received 2 doses of either HZ/su or placebo and did not develop a confirmed case of HZ within 1 month after the second dose); N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) in years; n/T (per 1000) = incidence rate of subjects reporting at least one event; 95% CI =95% confidence interval; LB = Lower Bound, UB = Upper Bound; VE (%) = Vaccine Efficacy (Poisson method)

Reviewer comment: *The incidence of HZ in the placebo group is higher than what is reported in the literature for patients receiving an HCT (approximately 40 – 60 per 1000 PY).*

6.1.11.2 Analyses of Secondary Endpoints

VE for reduction in duration of severe 'worst' pain

Severe 'worst' HZ-associated pain was defined as the subject's ZBPI response of at least 3 out of 10 to the question of the subject's worst HZ-associated pain. Of the 49 subjects with a confirmed HZ episode in the HZ/su group, 37 (75.5%) reported at least one day of severe 'worst' HZ-associated pain. These subjects had a median (minimum - maximum) duration of severe 'worst' pain of 14.0 days (1.0 – 178.0). Of the 135 subjects in the placebo group with a confirmed HZ episode, 120 (88.9%) reported at least one day with severe 'worst' HZ-associated pain. These subjects had a median (minimum – maximum) duration of severe 'worst' pain of 24.0 (1.0 – 1,025.0) days in the placebo group. The Applicant provides a VE in reduction in the occurrence of severe 'worst' pain among subjects with confirmed HZ of 38.5% (95% CI: 11.1, 57.5%).

Reviewer comment: *Please see the statistical review for issues with the statistical analysis of the vaccine efficacy for the reduction of severe 'worst' pain, which the statistical reviewer determined to be uninterpretable.*

VE in the reduction of confirmed HZ-associated complications

HZ-related complications (other than PHN) were reported in 16 subjects in the mTVC. Three subjects in the HZ/su group (6.1% of those with confirmed HZ) and 12 subjects in the placebo group (9.6% of those with confirmed HZ) reported cutaneous disseminated HZ. One subject in the placebo group reported HZ meningoencephalitis. No subjects reported more than one complication. VE for the reduction in HZ-related complications in all subjects in the mTVC was 77.8% (95% CI: 19.1, 95.9%).

Reviewer comment: *This is a descriptive analysis of a composite endpoint assessed on the overall study population. Not all HZ complications were observed in the study and benefit beyond prevention of HZ was not determined.*

VE in the prevention of PHN
In the mTVC, one subject in the HZ/su group (2.0% of those with confirmed HZ) and nine subjects in the placebo group (6.6% of those with confirmed HZ) reported PHN. VE for the prevention of PHN in all subjects in the mTVC was 89.3% (95% CI: 22.5, 99.8%). An exploratory endpoint was VE in the prevention of PHN in subjects with confirmed HZ, which was calculated to be 69.4% (95% CI: -77.4, 95.0%).

Reviewer comment: *A statistically significant benefit of HZ/su in the prevention of PHN in subjects with confirmed HZ was not demonstrated; however, there is a lower proportion of subjects with HZ who reported PHN in the HZ/su group compared to the placebo group, suggesting there may be a benefit in the prevention of PHN beyond prevention of HZ in this population.*

Humoral Immunogenicity
Anti-gE Ab concentrations as measured by the anti-gE ELISA at M0, M1, M2, M13, and M25 were secondary objectives.

Reviewer comment: *There is no humoral or cell-mediated vaccine-mediated immune correlate or surrogate of protection for HZ. However, humoral immune responses have been used to support regulatory decision-making regarding HZ/su lot-to-lot consistency, dose scheduling and concomitant administration of HZ/su and quadrivalent influenza vaccine. In addition, for the purposes of this sBLA the immune response to vaccination provides supportive information on vaccine effectiveness in a diverse population of IC adults. Therefore, humoral immune response was reviewed and will be presented here.*

Analyses were performed on the ATP cohort for humoral immunogenicity or the ATP cohort for persistence depending on time point. Of the subjects in the TVC, 201 were included in the TVC cohort for humoral Immunogenicity (10.9%). There were 82 subjects in the HZ/su group (81.2% of the TVC for humoral Immunogenicity) and 76 subjects in the placebo group (76.0% of the TVC for humoral Immunogenicity) included in the ATP cohort for humoral immunogenicity (Month 2). At Months 13 and 25, 5.5% and 3.7%, respectively, of the TVC were included in the ATP cohort for Humoral Persistence.

Reviewer comment: *The significance of persistence of humoral response in this population with regard to protection against HZ is not known.*

The majority of subjects in the HZ/su and placebo groups were seropositive for anti-gE antibodies pre-vaccination and all subsequent timepoints. In the HZ/su group, seropositivity peaked at 100% at M2, then returned to baseline (approximately 95%) by M25. In the placebo group, seropositivity varied between 80.0% at M13 and 89.5% at baseline.

Anti-gE Ab geometric mean concentrations (GMCs) for the HZ/su group are presented below. Anti-gE Ab GMCs for the placebo group were 555.0 mIU/mL (95% CI: 404.3, 761.8) at baseline and ranged from 443.8 mIU/mL – 556.6 mIU/mL at the post-vaccination time points.

Table 12. Geometric Mean Concentrations (GMCs) of anti-gE antibody ELISA in the HZ/su Group at Months 0, 1, 2, 13 and 25, Zoster-002 (Adapted ATP cohort for humoral immunogenicity)

Timing	N	GMC mIU/mL	GMC 95% CI (LB, UB)	Min	Max
Pre, Month 0	82	762.8	(568.6, 1023.5)	<97.0	23386.1
Month 1	78	1844.2	(1282.2, 2652.4)	<97.0	143121.1
Month 2	82	12753.2	(7973.0, 20399.4)	261.6	532820.0
Month 13	54	3183.8	(1869.8, 5421.2)	<97.0	255900.0
Month 25	39	2819.0	(1387.1, 5729.1)	<97.0	132826.2

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 34, p. 249
ATP = according to protocol; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; 95% CI = 95% confidence interval; LB = Lower Bound; UB = Upper Bound; Min/Max = Minimum/Maximum; Pre = pre-vaccination

The mean geometric increase (MGI) of anti-gE Ab concentrations over baseline at Months 1, 2, 13 and 25 in the HZ/su group were 2.5 (95% CI: 1.8, 3.5), 16.7 (95% CI: 10.0, 27.9), 4.5 (95% CI: 2.6, 7.9) and 4.4 (95% CI: 1.9, 10.0), respectively. In the placebo group, the MGI over baseline was not higher than 0.93 at any timepoint.

Vaccine response rates (VRRs) for anti-gE Ab concentrations at Months 1, 2, 13 and 25 in the HZ/su group were 29.5% (95% CI: 19.7, 40.9%), 67.1% (95% CI: 55.8, 77.1%), 40.4% (95% CI: 27.0, 54.9%) and 44.7% (95% CI: 28.6, 61.7%), respectively. In the placebo group, the VRR for anti-gE Ab concentrations (point estimate) was 0% at Months 1 and 2, and 8.9% and 14.8% at M13 and M25, respectively.

Reviewer comment: *AutoHCT subjects who received HZ/su demonstrated a humoral immune response to vaccination based on anti-gE Ab. This response was not as pronounced as the humoral response in the older adult population (GMC 52,376.6 and MGI 42.0 at one month post-vaccination) observed in the data submitted as part of the original BLA; however, vaccine efficacy was seen in this IC population (see section 6.1.11.1).*

Analyses of the TVC for humoral immunogenicity were performed, since more than 5% in both treatment groups at the applicable timepoints were excluded from the ATP cohort for humoral immunogenicity and Humoral persistence. These cohorts included 6.6 – 10.8% of the TVC. The results of these analyses were consistent with the results of the ATP analyses.

Humoral immune responses were presented by age stratum (18 – 49 YOA and ≥50 YOA) and underlying disease.

By age: The seropositivity rate for anti-gE Ab in the 18 – 49 YOA group was 100% in the HZ/su group (95% CI: 86.8, 100%) and 82.4% (95% CI: 56.6, 96.2%) in the placebo group pre-vaccination. Seropositivity in the younger age stratum remained above 92.9% at all times points post-vaccination in the HZ/su group and above 72.7% at all time points in the placebo group. Seropositivity in the ≥50 YOA stratum was similar at baseline between treatment groups (91.5 – 92.9%), peaking at 100% at M2 in the HZ/su group and remaining at approximately baseline thereafter; in the placebo group, seropositivity remained above 82.4% post-vaccination.

Reviewer comment: *A small number of subjects 18 – 49 YOA (26 in the HZ/su group and 17 in the placebo group pre-vaccination) contributed to this analysis and differences in seropositivity in this age stratum were not significant.*

Regarding the 18 – 49 YOA stratum, in the HZ/su group, the MGI of anti-gE Ab over pre-vaccination peaked at 12.4 (95% CI: 4.7, 32.8) at M2 and was 3.3 (95% CI: 1.2, 8.52) and 1.9 (95% CI: 0.6 – 6.2) at Months 13 and 25, respectively. Regarding the ≥50 YOA stratum, in the HZ/su group, the MGI over pre-vaccination peaked at 19.2 (95% CI: 10.4, 35.6) at M2, and was 5.4 (95% CI: 2.6, 11.0) and 6.7 (95% CI: 2.2, 20.6) at M13 and M25, respectively. For all age strata, in the placebo group, the MGI over pre-vaccination was not higher than 1.2 at any timepoint.

For the 18 – 49 YOA stratum, the VRR in the HZ/su group peaked at 57.7% (95% CI: 36.9, 76.6%) at M2, and was 33.3% (95% CI: 13.3, 59.0%) and 23.1% (95% CI: 5.0% – 53.8%) at M13 and M25, respectively. For the ≥50 YOA stratum, the VRR in the HZ/su group peaked at 71.4% (95% CI: 57.8, 82.7%), and was 44.1% (95% CI: 27.2, 62.1%) and 56.0% (95% CI: 34.9, 75.6%) at M13 and M25, respectively.

Reviewer comment: *The differences in the humoral immune response between the two age strata were not statistically significant. As noted above, immunogenicity is based upon small numbers of subjects in the 18 – 49 YOA age stratum. Differences in underlying diseases and therapies may also contribute to any differences in immunogenicity.*

Underlying disease: The Zoster-002 CSR presented humoral immunogenicity in the ATP cohort for immunogenicity by the underlying disease strata of multiple myeloma and all other diagnoses. Both groups demonstrated an anti-gE antibody response following vaccination. Humoral immune response was greater at M2 in the MM group compared to the 'other' diagnoses group based on anti-gE antibody GMC, MGI, and anti-gE VRR. In the Comprehensive Summary of Efficacy, a post hoc analysis on the mTVC by detailed underlying disease with 'other' separated into specific diagnoses is presented (see below).

Table 13. Geometric mean concentrations (GMCs) and vaccine response rate (VRR) of anti-gE antibody ELISA in the HZ/su group at months 0 and 2 by detailed underlying disease, Zoster-002 (mTVC)

Underlying Disease Subgroup	Timing	N	GMC	GMC 95% CI LB	GMC 95% CI UB	VRR N	VRR n	VRR %	VRR 95% CI LB	VRR 95% CI UB
MM	Pre, M0	468	470.6	415.6	532.8	-	-	-	-	-
	M2	444	32549.3	27585.8	38405.7	440	399	90.7	87.6	93.2
NHBCL	Pre, M0	235	822.7	728.2	929.4	-	-	-	-	-
	M2	227	1378.4	1124.4	1689.8	226	32	14.2	9.9	19.4
NHTCL	Pre, M0	42	1221.7	853.2	1749.2	-	-	-	-	-
	M2	40	11052.4	6179.4	19768.5	40	28	70.0	53.5	83.4
HL	Pre, M0	74	1114.9	829.0	1499.5	-	-	-	-	-
	M2	68	22744.4	13849.0	37353.5	68	51	75.0	63.0	84.7
AML	Pre, M0	20	759.2	519.7	1109.1	-	-	-	-	-
	M2	20	19597.6	9458.0	40607.5	20	17	85.0	62.1	96.8

Underlying Disease Subgroup	Timing	N	GMC	GMC 95% CI LB	GMC 95% CI UB	VRR N	VRR n	VRR %	VRR 95% CI LB	VRR 95% CI UB
Others	Pre, M0	24	735.6	480.5	1126.1	-	-	-	-	-
	M2	23	21120.6	8305.6	53708.3	23	16	69.6	47.1	86.8

Source: Adapted from 125614/398.0, Comprehensive Summary of Efficacy, Tables 74 and 75, pp. 177 – 178
mTVC = modified total vaccinated cohort; MM = multiple myeloma; NHBCL = non-Hodgkin B-Cell Lymphoma; NHTCL = non-Hodgkin T-Cell Lymphoma; HL = Hodgkin Lymphoma; AML = acute myeloid leukemia; Others = all other diseases; GMC = geometric mean ant body concentration calculated on all subjects; 95% CI = 95% confidence interval; LB = Lower Bound, UB = Upper Bound; VRR = vaccine response rate
Vaccine response defined as: For initially seronegative subjects, antibody concentration at post-vaccination ≥4-fold the cut-off for anti-gE (4x97 mIU/mL); For initially seropositive subjects, antibody concentration at post-vaccination ≥4-fold the pre-vaccination antibody concentration
N = Number of subjects with pre- and post-vaccination results available; n/% = Number/percentage of responders; Pre = pre-vaccination; M = month

Subjects with MM tended to show the greatest anti-gE antibody response based on GMCs and VRRs at M2, while subjects with non-Hodgkin T cell lymphoma (NHTCL), Hodgkin Lymphoma, acute myeloid leukemia (AML) and other underlying diseases were within the same range for anti-gE antibody GMC and VRR. Subjects with non-Hodgkin B cell lymphoma (NHBCL) had the lowest anti-gE antibody GMCs and VRRs.

Reviewer comment: *Despite low immune responses in subjects with NHBCL, VE was 60.5% (95% CI: 31.0, 78.2), indicating that anti-gE antibody does not predict efficacy in this group (see section 6.1.11.3).*

6.1.11.3 Subpopulation Analyses

HZ VE by age
HZ VE by age group is presented below.

Table 14. Vaccine efficacy: First or only episode of HZ during the entire study period by age strata using Poisson method, Zoster-002 (mTVC)

Type	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LB 95% CI	VE UB 95% CI
18 – 49 YOA	213	9	419.4	21.5	212	29	381.4	76.0	71.8	38.7	88.3
≥50 YOA	657	40	1213.7	33.0	639	106	1050.5	100.9	67.3	52.6	77.9

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 7.2, p. 1698
mTVC = modified total vaccinated cohort (subjects who received 2 doses of either HZ/su or placebo and did not develop a confirmed case of HZ within 1 month after the second dose); N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) in years; n/T (per 1000) = incidence rate of subjects reporting at least one event; 95% CI = 95% confidence interval; LB = Lower Bound, UB = Upper Bound; VE (%) = Vaccine Efficacy (Poisson method); YOA = years of age

Reviewer comment: *HZ VE was demonstrated in both age strata. HZ VE in younger post-autoHCT subjects was slightly higher with wider CIs than HZ VE in post-autoHCT subjects 50 YOA and older; there were fewer subjects in this age stratum contributing to the analysis.*

HZ VE by underlying disease
The Applicant presented an analysis of HZ VE by underlying disease (MM or 'other') in the CSR.

- Multiple myeloma: 72.4% (95% CI: 54.8% – 83.7%)
- Other diagnoses: 63.6% (95% CI: 42.3% – 77.7%)

A post hoc analysis by detailed underlying disease was presented in the Comprehensive Summary of Efficacy and is shown below.

Table 15. Vaccine efficacy: First or only episode of HZ during the entire study period by detailed underlying disease category using Poisson method, Zoster-002 (mTVC)

Underlying disease subgroup	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LB 95% CI	VE UB 95% CI
MM	472	22	907.2	24.2	465	69	786.7	87.7	72.4	54.8	83.7
NHBCL	237	19	438.5	43.3	244	45	410.6	109.6	60.5	31.0	78.2
NHTCL	43	1	78.9	12.7	40	5	69.2	72.3	82.5	-56.8	99.6
HL	74	5	136.9	36.5	60	7	110.2	63.5	42.5	-110.4	85.6
AML	20	0	32.2	0.0	16	3	19.8	151.4	100.0	-48.9	100.0
Other	24	2	39.4	50.8	26	6	35.4	169.4	70.0	-67.8	97.0

Source: Adapted from 125614/398.0, Comprehensive Summary of Efficacy, Appendix Table 52, p. 164
mTVC = modified vaccinated cohort; MM = multiple myeloma; NHBCL = non-Hodgkin B-Cell Lymphoma; NHTCL = non-Hodgkin T-Cell Lymphoma; HL = Hodgkin Lymphoma; AML = acute myeloid leukemia; Others = all other diseases; N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) in years; n/T (per 1000) = incidence rate of subjects reporting at least one event; 95% CI = 95% confidence interval; LB = Lower Bound, UB = Upper Bound
VE (%) = Vaccine Efficacy (Poisson method)

Reviewer comment: *This analysis is based on small numbers of subjects enrolled for NHTCL, Hodgkin Lymphoma, AML and other, so conclusions cannot be drawn regarding VE in these groups. HZ VE was demonstrated in subjects with MM, as well as NHBCL, for whom a robust humoral response was not seen (see section 6.1.11.2).*

A post hoc analysis of VE in subjects treated with bortezomib was not performed due to a small number of subjects, 13.9% of subjects in each group receiving this therapy. At CBER's request the Applicant performed this analysis and VE was similar to the entire study population.

<u>HZ VE by antiviral prophylaxis and region</u>
The Applicant presented an analysis of HZ VE by anticipated use of HZ prophylactic antiviral therapy (PAT) at the beginning of the study. For subjects who received PAT in the HZ/su group, the median (min-max) duration was 57.0 (1.0 – 1121.0) days in the HZ/su group and 53.0 (1 – 1,442 days) days in the placebo group. A post hoc analysis of HZ VE by actual duration of PAT is presented below. VE was similar for subjects not receiving PAT (72.6%; 95% CI: 57.1, 83.0) and subjects receiving up to 60 days of PAT (72.5%; 95% CI: 44.0, 87.7). For subjects who received >60 days of PAT, VE was 37.8% (95% CI: -42.3, 73.4).

Table 16. Vaccine Efficacy: First or only episode of HZ during the entire study period by the use of Prophylactic Antiviral Therapy (PAT) duration during the entire study period using Poisson method, Zoster-002 (mTVC)

Actual PAT Duration	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%) 95% CI	VE LB 95% CI	VE UB 95% CI
No PAT	454	27	852.6	31.7	426	80	693.2	115.4	72.6	57.1	83.0
1-60 days	226	10	408.1	24.5	262	40	449.4	89.0	72.5	44.0	87.7
≥60 days	190	12	372.3	32.2	163	15	289.3	51.8	37.8	-42.3	73.4

Source: Adapted from 125614/398.0, Comprehensive Summary of Efficacy, Appendix Table 51, p. 164

mTVC = modified total vaccinated cohort; PAT = Prophylactic Antiviral Therapy; N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; n/T (per 1000) = incidence rate of subjects reporting at least one event; 95% CI = 95% confidence interval; LB = Lower Bound, UB = Upper Bound; VE (%) = Vaccine Efficacy (Poisson method)

Reviewer comment: *In the US, standard of care in post-autoHCT is generally to receive PAT for one-year post-transplant. In -002, individuals anticipated to receive PAT for >6 months were not enrolled. Only approximately 20% of subjects received PAT for HZ for more than 60 days, and in those subjects VE against HZ was not demonstrated. However, the study was not powered to evaluate efficacy by use of PAT.*

A post hoc analysis of HZ VE by region was performed. There were no cases of HZ in South America. The VE against HZ across Europe was 60.8% (95% CI: 41.2, 74.3), North America was 59.9% (95% CI: 3.0, 84.9) and Austrasia was 88.2% (95% CI: 69.9, 96.4).

Reviewer comment: *The majority (82.8%) of subjects enrolled in North America were enrolled at US sites. The VE point estimate in North America was consistent with Europe, but with a wide CI and a LB of the 95% CI of 3.0%. The VE point estimate in Austrasia was higher than Europe and North America. The study was not designed to evaluate VE by racial subgroups. Variations in immunosuppressive therapies, PAT, and underlying disease in subjects enrolled in different regions may contribute to differences observed by race.*

HZ VE by gender
The VE by gender is presented below.

Table 17. Vaccine efficacy: First or only episode of HZ during the entire study period by gender using Poisson method, Zoster-002 (mTVC)

Gender	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LB 95% CI	VE UB 95% CI
Female	323	16	614.3	26.0	317	61	524.6	116.3	71.77	38.8	88.3
Male	547	33	1018.8	32.4	534	74	907.3	81.6	60.28	39.4	74.5

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 7.5, p. 1704
mTVC = modified total vaccinated cohort; N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; n/T (per 1000) = incidence rate of subjects reporting at least one event; 95% CI = 95% confidence interval; LB = Lower Bound, UB = Upper Bound; VE (%) = Vaccine Efficacy (Poisson method)

Reviewer comment: *HZ VE was demonstrated in both male and female autoHCT recipients. The HZ VE in males trended lower with a slightly narrower CI than in females. This difference was not observed in the older adult population.*

HZ VE by race and ethnicity
At CBER's request, in response to an IR, the Applicant provided an analysis of VE by ethnicity and race/geographic ancestry with subjects grouped into four broader subgroups: African (African heritage/African American), Asian (Central/South Asian heritage, East Asian heritage, Japanese heritage or Southeast Asian heritage), White (Caucasian/European heritage or of Arabic/North African heritage), and Other (American Indian, Alaskan native, Native Hawaiian, Pacific Islander or Other).

Table 18. Vaccine efficacy first or only episode of HZ during the entire study period by geographic ancestry and ethnicity, Zoster-002 (mTVC)

Characteristic	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LB 95% CI	VE UB 95% CI
Race											
African	15	0	29.2	0.0	23	4	32.5	123.0	100.0	-68.6	100.0
Asian	138	2	270.6	7.4	139	29	216.3	134.1	94.5	78.2	99.4
White	686	45	1277.7	35.2	666	99	1140.0	86.8	59.5	41.8	72.2
Other	31	2	55.6	36.0	23	3	43.1	69.6	48.3	-351.2	95.7
Ethnicity											
American, Hispanic or Latino subjects	24	0	43.5	0.0	25	3	39.4	76.0	100.0	-119.4	100.0
Not American Hispanic or Latino subjects	846	49	1589.6	30.8	826	132	1392.5	94.8	67.5	54.5	77.1

Source: Adapted from 125614/398.11, Response to IR received on June 7, 2021, Question 1, Table 1, p. 1; and 125614/398.9, Response to IR received on April 22, 2012, Question 5, Table 1, p. 7
mTVC = modified total vaccinated cohort
African = African Heritage / African American
Asian and White Geographic Ancestries combine more than one of the Applicant's groups.
Asian = Central/South Asian, East Asian, South East Asian and Japanese Heritage
White = Arabic/North African and Caucasian/European Heritage
Other = American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, and Other
N = number of subjects; n/% = number/percentage of subjects with at least one event; T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; n/T (per 1000) = incidence rate of subjects reporting at least one event; 95% CI = 95% confidence interval; LB = Lower Bound, UB = Upper Bound; VE (%) = Vaccine Efficacy (Poisson method)

Reviewer comment: *VE against HZ was demonstrated in White and Asian subjects with Asian subjects having a higher VE than White subjects in this post-hoc analysis. This difference by race was not observed in the older adult studies. The study was not designed to evaluate VE by racial subgroups and lacks power to draw conclusions about VE in each of these subgroups. Differences observed between groups may be attributed to variations in immunosuppressive therapies, PAT, and underlying disease in subjects enrolled in different regions.*

6.1.11.4 Dropouts and/or Discontinuations

The mTVC included 93% of the subjects in the TVC and the proportion of subjects who withdrew was not unexpected based on underlying diseases and therapies. Results of efficacy analyses performed on the TVC were consistent with the analyses on the mTVC.

6.1.11.5 Exploratory and Post Hoc Analyses

HZ VE over one-year post-HCT

A pre-specified tertiary endpoint was HZ VE during the one-year post-transplant period, presented below. The median follow-up time after vaccination was 7.7 months in the HZ/su group and 7.6 months in the placebo group.

Table 19. Vaccine efficacy: First or only episode of HZ during 365 days post-Hematopoietic stem Cell Transplant (HCT) using Poisson method, Zoster-002 (mTVC)

Type	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LB 95% CI	VE UB 95% CI
OVERALL	870	21	516.2	40.7	851	82	480.6	170.6	76.15	61.1	86.0

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 7.8, p. 1706
mTVC = modified total vaccinated cohort; N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) in years; n/T (per 1000) = incidence rate of subjects reporting at least one event; 95% CI =95% confidence interval; LB = Lower Bound, UB = Upper Bound; VE (%) = Vaccine Efficacy (Poisson method)

Reviewer comment: *VE was demonstrated in the post-autoHCT population during the one-year post-transplant, the time period they are at greatest risk for HZ. HZ VE during the entire study period was only slightly lower (68.2%, 95% CI: 55.6, 77.5%), indicating there is persistence of efficacy through the approximately 21-month median follow-up time.*

Other clinical tertiary endpoints: In addition to the above-described endpoints, the Applicant assessed as exploratory endpoints the VE in reduction of overall mortality, HZ-related mortality, overall hospitalizations, HZ-related hospitalizations, and duration of pain medications in autoHCT subjects. No subjects in the study died due to HZ. Two subjects in the HZ/su group (4.1% of subjects with confirmed HZ) and 13 subjects in the placebo group (9.6% of subjects with confirmed HZ) reported an HZ-related hospitalization, and none reported more than one HZ-related hospitalization. The VE in all subjects against first or only episode of confirmed HZ-related hospitalizations during the entire study period using the Cox regression method was 84.70% (95% CI: 32.2, 96.6%). VE for overall hospitalizations was not provided in the CSR. Other VE calculations had a LB <0.

Reviewer comment: *The VE for HZ-related hospitalizations was calculated including all subjects, not only confirmed HZ cases. VE in prevention of HZ-related hospitalization in only subjects with confirmed HZ was not assessed.*

Cell-mediated Immunogenicity (CMI)
In the HZ/su group of the Adapted ATP cohort for immunogenicity – CMI, the median (min - max) fold increase over pre-vaccination in the frequency of gE-specific CD4 T-cells was 8.2 (0.0 – 3486.5), 109.0 (0.0 – 24677.3), 43.6 (0.0 – 7502.6) and 50.9 (0.3 – 3126.4) at Months 1, 2, 13 and 25. In the placebo group, the observed median fold increase over pre-vaccination was not higher than 2.1 at any timepoint.

In the HZ/su group, the VRR (defined as at least a two-fold increase in T cell frequencies compared to the threshold or pre-vaccination frequencies for subjects with pre-vaccination frequencies below or above threshold, respectively) in the frequency of gE-specific CD4 T-cells was 46.3% (95% CI: 30.7, 62.6), 92.9% (95% CI: 80.5, 98.5), 70.4% (95% CI: 49.8% – 86.2%) and 70.8% (95% CI: 48.9% – 87.4%) at Months 1, 2, 13 and 25. In the placebo group, the VRR point estimate was not higher than 12.5% at any timepoint.

Reviewer comment: *A cellular immune response was seen in post-autoHCT subjects. Although not presented here, this response was consistent in both the 18 – 49 and ≥50 YOA strata. In a post-hoc analysis of CMI by detailed underlying disease, a cell-mediated response to vaccination was observed in NHBCL subjects, a group which did not show a humoral response to vaccination.*

6.1.12 Safety Analyses

6.1.12.1 Methods

Descriptive safety analyses were performed on the TVC and are presented below. Please see section 6.1.7 for an overview of the assessment of safety.

6.1.12.2 Overview of Adverse Events

The TVC, the primary population for the assessment of safety, included 1846 subjects total, 922 in the HZ/su group and 924 in the placebo group.

For all subjects in the TVC, the median safety follow-up time was approximately 29 months, with approximately 29 months in the HZ/su group and approximately 28 months in the placebo group. In both groups, the maximum follow-up time was 52 months.

Solicited Adverse Events
Compliance with return of local symptom sheets and general symptom sheets for reactogenicity assessments for both treatment groups was above 95% (range 95.8% – 97.2%) following each dose and overall. Compliance with symptom sheet return by age strata was reviewed and was 94.8% or greater for each age stratum, symptom screener (local or general), dose, and treatment group.

Overall solicited AEs: Overall by subject, both doses considered, 89.7% and 53.2% of subjects in the HZ/su and placebo groups, respectively, reported at least one solicited symptom of any grade during the seven-day post-vaccination period. At least one local symptom was reported by 85.8% and 10.4% of subjects in the HZ/su and placebo groups, respectively, and at least one general symptom was reported by 75.2% and 50.9% of subjects in the HZ/su and placebo groups, respectively. The percentage of subjects in the HZ/su group reporting any solicited symptom, any solicited local symptom, and any solicited general symptom after dose 1 as compared to dose 2 was 84.5% vs. 84.8%, 78.8% vs. 78.2%, and 59.2% vs. 66.0%, respectively.

Reviewer comment: *In this post autoHCT population, half of subjects in the placebo group report general symptoms. Both local and general symptoms were reported at greater rates in the HZ/su group. The proportions of subjects reporting any grade of solicited symptoms and any grade local solicited symptoms in the HZ/su group was comparable following dose 1 as compared to dose 2. Proportions of subjects in the HZ/su group reporting solicited general symptoms was slightly higher following dose 2 compared to dose 1.*

The proportions of HZ/su recipients reporting any (Grade 1 or greater) solicited symptom during the 7-day post-vaccination period by age strata overall by subject, both doses considered, was 91.5% and 89.1% for the age strata 18 – 49 YOA and ≥50 YOA, respectively. The percentage of HZ/su recipients reporting any local solicited symptoms during the 7-day post-vaccination period was 87.9% and 85.1% for the age strata 18 – 49 YOA and ≥50 YOA, respectively. The percentage of HZ/su recipients reporting any general solicited symptom during the 7-day post-vaccination period was 79.4% and 73.9% for the age strata 18 – 49 YOA and ≥50 YOA, respectively. Slightly more subjects in the HZ/su group in both age strata reported any general solicited symptom following dose 2 compared to dose 1 (64.4% vs. 72.4% in subjects 18 – 49 YOA and 57.4% vs. 64% in subjects ≥50 YOA following dose 1 and dose 2, respectively).

Reviewer comment: *In this post-autoHCT population, the proportions of subjects reporting any, any local, or any general solicited symptom in the HZ/su group was similar in the younger and older age strata. There was a trend toward higher proportions of solicited symptoms reported in the younger age group, though this was not as apparent as in the immunocompetent older adult population. In both age strata, solicited general symptoms were reported slightly more frequently following dose 2.*

Overall by subject, both doses considered, 21.1% and 6.3% of subjects in the HZ/su and placebo groups, respectively, reported a Grade 3 solicited symptom. At least one Grade 3 solicited local symptom was reported by 14.2% and 0.3% of subjects in the HZ/su and placebo groups, respectively, and at least one Grade 3 solicited general symptom was reported by 13.2% and 6.0% of subjects in the HZ/su and placebo groups, respectively. The percentage of subjects in the HZ/su group reporting any Grade 3 solicited symptom, any Grade 3 solicited local symptom, and any Grade 3 solicited general symptom after dose 1 as compared to dose 2 was 10.7% vs. 16.4%, 7.4% vs. 10.5%, and 5.8% vs. 10.2% respectively.

Overall by subject and by age in the HZ/su group, both doses considered, 27.7% and 18.9% of HZ/su recipients 18 – 49 YOA and ≥50 YOA reported at least one Grade 3 solicited symptom. At least one Grade 3 solicited local symptom was reported by 18.8%, and 12.7% of HZ/su recipients 18 – 49 YOA and ≥50 YOA respectively, while at least one Grade 3 solicited general symptom was reported by 18.4%, and 11.5% of HZ/su recipients 18 – 49 YOA and ≥50 YOA, respectively. For the 18 – 49 YOA stratum, the proportion of subjects reporting any Grade 3 solicited symptoms increased and any Grade 3 solicited general symptoms following dose 2 compared to dose 1; Grade 3 solicited local symptoms did not increase with dose number in this age stratum. For ≥50 YOA stratum, any Grade 3 solicited symptoms, any Grade 3 local symptoms, and any Grade 3 solicited general symptoms increased following dose 2 compared to dose 1.

Reviewer comment: *Overall by subject in this autoHCT population, Grade 3 reactogenicity was common in both age strata following HZ/su administration and tended to be higher in the younger age stratum. For both age strata, grade 3 solicited AEs, both local and general, were reported at higher rates after dose 2 compared to dose 1. In the younger age stratum, this post-dose 2 increase was driven by an increase in Grade 3 general solicited symptoms only.*

The Applicant performed an analysis of the proportions of subjects reporting solicited symptoms lasting beyond the seven-day post-vaccination period. Overall per subject, both doses considered, 18.7%, 5.3% and 15.7% of HZ/su recipients reported at least one solicited symptom, solicited local symptom, and solicited general symptom, respectively, beginning in and lasting beyond the 7-day solicited reporting period. Overall per subject, 4.2%, 1.6% and 2.8% of HZ/su recipients reported at least one Grade 3 solicited symptom, Grade 3 solicited local, and Grade 3 solicited general symptom, respectively, beginning in and lasting beyond this period.

Reviewer comment: *The proportion of subjects reporting general solicited symptoms lasting beyond the seven-day assessment period is similar to that reported in the placebo group (17.9%) and so may be due to the underlying medical conditions in this study population.*

Solicited local symptoms: Overall by subject, both doses considered, at least one solicited local symptom was reported by 85.8% and 10.4% of subjects in the HZ/su group and placebo group, respectively, and at least one Grade 3 solicited local symptom was reported by14.2% and 0.3% of subjects in the HZ/su and placebo groups, respectively. The numbers and proportions of

subjects in the TVC reporting any grade and Grade 3 individual solicited local symptoms are below.

Table 20. Incidence of solicited local symptoms reported during the 7-day post-vaccination period overall by subject, both doses considered, Zoster-002 (TVC)

Solicited Symptom	Grade	HZ/su N	HZ/su n	HZ/su %	Placebo N	Placebo n	Placebo %
Pain	Any	901	756	83.9	892	83	9.3
	Grade 3	901	99	11.0	892	3	0.3
Redness (mm)	Any grade	901	301	33.4	892	9	1.0
	>100	901	28	3.1	892	0	0.0
Swelling (mm)	Any grade	901	168	18.6	892	9	1.0
	>100	901	13	1.4	892	0	0.0

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 42
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n/% = number/percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
Any grade redness and swelling includes subjects with events measured ≥20 mm, or reported as present with missing measurements.

Overall by subject, pain was the most commonly reported local solicited symptom reported by subjects in both the HZ/su and placebo groups (83.9% and 9.3% of subjects, respectively). The table below shows the number and proportion of subjects in the HZ/su group reporting any grade and Grade 3 individual solicited local symptoms following dose 1 and 2.

Table 21. Incidence of solicited local symptoms reported in the HZ/su group during the 7-day post-vaccination period following dose 1 and dose 2 overall by subject, Zoster-002 (TVC)

Solicited Symptom	Grade	Dose 1 N	Dose 1 n	Dose 1 %	Dose 2 N	Dose2 n	Dose2 %
Pain	Any	896	688	76.8	840	638	76.0
	Grade 3	896	59	6.6	840	63	7.5
Redness (mm)	Any grade	896	187	20.9	840	231	27.5
	>100	896	7	0.8	840	24	2.9
Swelling (mm)	Any grade	896	101	11.3	840	132	15.7
	>100	896	1	0.1	840	12	1.4

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 42
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n/% = number/percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
Any grade redness and swelling includes subjects with events measured ≥20 mm, or reported as present with missing measurements.

Reviewer comment: *As stated above, the proportion of subjects in the HZ/su group reporting any local solicited symptom did not increase following dose 2, compared to dose 1. Similarly, the proportion of subjects reporting any pain and Grade 3 pain was generally similar following dose 2 compared to dose 1. However, the proportion of subjects reporting any and Grade 3 redness or swelling did increase after dose 2 compared to dose 1. The proportion of subjects reporting grade 3 redness and swelling was less than 5% following each dose.*

The maximum redness reported was 20.0 cm in a 64 YO female, which was resolving 7 days following dose 2 of HZ/su (resolution not reported). The maximum swelling reported was 14.0 cm in a 40 YO woman, which had resolved on day 8 after dose 2 of HZ/su. Seven subjects in the HZ/su group and three subjects in the placebo group reported unsolicited local injection site reactions. In the HZ/su group this included injection site rash, pruritis, pain, and mass. All were mild, except for one subject reporting severe injection site pain (verbatim term “soreness”) and resolved within 12 days or less.

The proportions of subjects in each treatment group reporting individual local symptoms (any grade and Grade 3) overall by age strata with both doses considered and overall by age strata and dose number are presented below.

Table 22. Incidence of solicited local symptoms reported during the 7-day post-vaccination period overall by subject, both doses considered, by age strata, Zoster-002 (TVC)

Solicited Symptom	Grade	HZ/su 18 – 49 YOA N=224 n (%)	Placebo 18 – 49 YOA N=219 n (%)	HZ/su ≥50 YOA N=677 n (%)	Placebo ≥50 YOA N=673 n (%)
Pain	Any	196 (87.5)	24 (11.0)	560 (82.7)	59 (8.8)
	Grade 3	37 (16.5)	1 (0.5)	62 (9.2)	2 (0.3)
Redness (mm)	Any grade	67 (29.9)	0 (0)	234 (34.6)	9 (1.3)
	>100	6 (2.7)	0 (0)	22 (3.2)	0 (0)
Swelling (mm)	Any grade	46 (20.5)	0 (0)	122 (18.0)	9 (1.3)
	>100	4 (1.8)	0 (0)	9 (1.3)	0 (0)

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 10.76, pp. 2427 - 2428
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n (%) = number/percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
Any grade redness and swelling includes subjects with events measured ≥20 mm, or reported as present with missing measurements.

Table 23. Incidence of solicited local symptoms reported during the 7-day post-vaccination period overall by subject, by age strata and dose number, Zoster-002 (TVC)

Solicited Symptom	Grade	HZ/su 18 – 49 YOA Dose 1 N=223 n (%)	HZ/su 18 – 49 YOA Dose 2 N=205 n (%)	Placebo 18 – 49 YOA Dose 1 N=217 n (%)	Placebo 18 – 49 YOA Dose 2 N=207 n (%)	HZ/su ≥50 YOA Dose 1 N=673 n (%)	HZ/su ≥50 YOA Dose 2 N=635 n (%)	Placebo ≥50 YOA Dose 1 N=673 n (%)	Placebo ≥50 YOA Dose 2 N=627 n (%)
Pain	Any	181(81.2)	168 (82.0)	17 (7.8)	13 (6.3)	507 (75.3)	470 (74.0)	39 (5.8)	32 (5.1)
	Grade 3	25 (11.2)	22 (10.7)	1 (0.5)	0	34 (5.1)	41 (6.5)	2 (0.3)	0
Redness	Any	44 (19.7)	52 (25.4)	0	0	143 (21.2)	179 (28.2)	5 (0.7)	4 (0.6)
	>100 mm	2 (0.9)	5 (2.4)	0	0	5 (0.7)	19 (3.0)	0	0
Swelling	Any	31 (13.9)	34 (16.6)	0	0	70 (10.4)	98 (15.4)	7 (1.0)	3 (0.5)
	>100 mm	0	4 (2.0)	0	0	1 (0.1)	8 (1.3)	0	0

Source: Adapted from 125614/398.0 Zoster-002 CSR, Table 10.76, pp. 2427 - 2428
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n (%) = number/percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
Any redness and swelling includes subjects with events measured ≥20 mm, or reported as present with missing measurements.

Reviewer comment: *By age strata, in this post-autoHCT population, approximately the same proportion of subjects in the HZ/su groups reported each individual local solicited symptom in the younger and older age strata. There was a slight decrease in the incidence of any and a decrease in the incidence of Grade 3 pain with increasing age, which is consistent with what was seen in the immunocompetent older adult population. In both age strata, reports of any and Grade 3 redness and any and Grade 3 swelling increased following dose 2 compared to dose 1, though the number of reports of Grade 3 redness and swelling was low overall.*

The Applicant presented solicited local symptoms by underlying diagnosis (MM and 'other diagnoses'). Trends in these groups were similar to that presented above.

Reviewer comment: *Overall by subject*, both doses considered, *Grade 3 pain was reported more frequently following HZ/su in subjects with 'other diagnoses' (14.1%) compared to MM (8.3%), which may be explained by the younger age of subjects with 'other diagnoses.'*

Overall per dose, the mean (median) duration of pain, redness or swelling reported after HZ/su administration was 3.3 (3.0), 3.6 (3.0) and 3.1 (2.0) days, respectively. The maximum duration of pain, redness, and swelling in the reported after HZ/su administration was 56, 33, and 15 days.

Solicited general symptoms: Overall by subject, both doses considered, at least one solicited general symptom was reported by 75.2% and 50.9% of subjects in the HZ/su group and placebo group, respectively and at least one Grade 3 solicited local symptom was reported 13.2% and 6.0% of subjects in the HZ/su and placebo groups, respectively. The numbers and proportions of subjects in the TVC reporting any grade and Grade 3 individual solicited local symptoms are below.

Table 24. Incidence of solicited general symptoms reported during the 7-day post-vaccination period overall by subject, both doses considered, Zoster-002 (TVC)

Solicited Symptom	Grade	HZ/su N	HZ/su n	HZ/su %	Placebo N	Placebo n	Placebo %
Fatigue	All	901	508	56.4	894	340	38.0
	Grade 3	901	66	7.3	894	31	3.5
Gastrointestinal symptoms	All	901	238	26.4	894	183	20.5
	Grade 3	901	18	2.0	894	17	1.9
Headache	All	901	302	33.5	894	166	18.6
	Grade 3	901	26	2.9	894	10	1.1
Myalgia	All	901	484	53.7	894	234	26.2
	Grade 3	901	56	6.2	894	19	2.1
Shivering	All	901	237	26.3	894	115	12.9
	Grade 3	901	35	3.9	894	7	0.8
Temperature	All*	901	183	20.3	894	50	5.6
	>39†	901	7	0.8	894	2	0.2
	>39.5†	901	3	0.3	894	1	0.1

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 43, pp. 270 - 274
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n/% = number/percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
* Fever defined as ≥37.5°C for oral, axillary, or tympanic route or ≥38°C for rectal route.
† Temperature as assessed via any route (oral, axillary, rectal, or tympanic)

Overall by subject, both doses considered, the most commonly reported local solicited symptoms reported by subjects in both the HZ/su and placebo groups were fatigue (56.4% and

38.0% of subjects, respectively) and myalgia (53.7% and 26.2%, respectively). The most frequently reported Grade 3 solicited general adverse events were also fatigue and myalgia. All solicited general adverse events of any grade were reported more frequently in the HZ/su group compared to the placebo group.

The table below shows the number and proportion of subjects in the HZ/su group reporting any grade and Grade 3 individual solicited general symptoms following dose 1 and 2.

Table 25. Incidence of solicited local symptoms reported in the HZ/su group during the 7-day post-vaccination period following dose 1 and dose 2 overall by subject, Zoster-002 (TVC)

Solicited Symptom	Grade	Dose 1 N	Dose 1 n	Dose 1 %	Dose 2 N	Dose2 n	Dose2 %
Fatigue	All	896	356	39.7	836	395	47.2
	Grade 3	896	30	3.3	836	48	5.7
Gastrointestinal symptoms	All	896	150	16.7	836	142	17.0
	Grade 3	896	6	0.7	836	13	1.6
Headache	All	896	156	17.4	836	232	27.8
	Grade 3	896	2	0.2	836	24	2.9
Myalgia	All	896	340	37.9	836	374	44.7
	Grade 3	896	22	2.5	836	42	5.0
Shivering	All	896	116	12.9	836	185	22.1
	Grade 3	896	6	0.7	836	29	3.5
Temperature	All*	896	60	6.7	836	150	17.9
	>39†	896	3	0.3	836	4	0.5
	>39.5†	896	1	0.1	836	2	0.2

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 43, pp. 270 - 274
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n/% = number/percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
* Fever defined as ≥37.5°C for oral, axillary, or tympanic route or ≥38°C for rectal route.
† Temperature as assessed via any route (oral, axillary, rectal, or tympanic)

Reviewer comment: *With the exception of gastrointestinal symptoms, all individual solicited general symptoms were reported by subjects in the HZ/su group at increased frequency following dose 2 compared to dose 1.*

The Applicant did not specify a Grade 4 for solicited AEs in their protocol. FDA guidance suggests fever >40°C is a Grade 4 (potentially life threatening) (Food and Drug Administration 2007). One subject, A 53 YOA man with multiple myeloma who received HZ/su reported a fever of 41.3°C on the day of dose 2. The fever was assessed as related, was not medically attended and had resolved the following day. This subject reported a mild temperature elevation to 37.8°C (orally) the day of dose 1. In 125614/398.9, the Applicant confirmed that the investigator thought the temperature was accurate and that the subject had a history of fevers well-controlled with paracetamol. No other fevers >40°C were reported in the study.

Reviewer comment: *Although one subject reported a temperature >40°C, few subjects (n=4 HZ/su subjects and n=6 placebo subjects) reported temperatures >39° C post-vaccination.*

The proportions of subjects in each treatment group reporting individual general symptoms (any grade and Grade 3) overall by age strata with both doses considered are presented below.

Table 26. Incidence of solicited general symptoms reported during the 7-day post-vaccination period overall by subject by age strata, both doses considered, Zoster-002 (TVC)

Solicited Symptom	Grade	HZ/su 18 – 49 YOA N=223 n (%)	Placebo 18 – 49 YOA N=220 n (%)	HZ/su ≥50 YOA N=678 n (%)	Placebo ≥50 YOA N=674 n (%)
Fatigue	All	143 (64.1)	87 (39.5)	365 (53.8)	253 (37.5)
	Grade 3	27 (12.1)	6 (2.7)	39 (5.8)	25 (3.7)
Gastrointestinal symptoms	All	47 (21.1)	40 (18.2)	191 (28.2)	143 (21.2)
	Grade 3	4 (1.8)	2 (0.9)	14 (2.1)	15 (2.2)
Headache	All	98 (43.9)	53 (24.1)	204 (30.1)	113 (16.8)
	Grade 3	11 (4.9)	4 (1.8)	15 (2.2)	6 (0.9)
Myalgia	All	129 (57.8)	61 (27.7)	355 (52.4)	173 (25.7)
	Grade 3	22 (9.9)	7 (3.2)	34 (5.0)	12 (1.8)
Shivering	All	70 (31.4)	35 (15.9)	167 (24.6)	80 (11.9)
	Grade 3	16 (7.2)	0 (0)	19 (2.8)	7 (1.0)
Temperature	All*	62 (27.8)	12 (5.5)	121 (17.8)	38 (5.6)
	>39†	4 (1.8)	0 (0)	3 (0.4)	2 (0.3)
	>39.5†	1 (0.4)	0 (0)	2 (0.3)	1 (0.1)

Source: Adapted from 125614/398.0 Zoster-002 CSR, Table 10.77, pp. 2429 - 2439; and Table 10.78, p. 2440
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n (%) = number/percentage of subjects reporting the symptom or the symptom of Grade 3 at least once; YOA = years of age
* Fever defined as ≥37.5°C for oral, axillary, or tympanic route or ≥38°C for rectal route.
† Temperature as assessed via any route (oral, axillary, rectal, or tympanic)

Table 27. Incidence of solicited general symptoms reported during the 7-day post-vaccination period overall by subject by age strata and dose number, Zoster-002 (TVC)

Solicited Symptom	Grade	HZ/su 18 – 49 YOA Dose 1 N=222 n (%)	HZ/su 18 – 49 YOA Dose 2 N=203 n (%)	Placebo 18 – 49 YOA Dose 1 N=218 n (%)	Placebo 18 – 49 YOA Dose 2 N=207 n (%)	HZ/su ≥50 YOA Dose 1 N=674 n (%)	HZ/su ≥50 YOA Dose 2 N=633 n (%)	Placebo ≥50 YOA Dose 1 N=674 n (%)	Placebo ≥50 YOA Dose 2 N=628 n (%)
Fatigue	All	108 (48.6)	104 (51.2)	74 (33.9)	52 (25.1)	248 (36.8)	291 (46.0)	208 (30.9)	160 (25.5)
	Grade 3	13 (5.9)	21 (10.3)	3 (1.4)	4 (1.9)	17 (2.5)	27 (4.3)	13 (1.9)	16 (2.5)
Gastrointestinal symptoms	All	32 (14.4)	26 (12.8)	28 (12.8)	25 (12.1)	118 (17.5)	116 (18.3)	106 (15.7)	73 (11.6)
	Grade 3	2 (0.9)	2 (1.0)	0	2 (1.0)	4 (0.6)	11 (1.7)	7 (1.0)	10 (1.6)
Headache	All	52 (23.4)	77 (37.9)	37 (17.0)	36 (17.4)	104 (15.4)	155 (24.5)	84 (12.5)	52 (8.3)
	Grade 3	1 (0.5)	10 (4.9)	0	4 (1.9)	1 (0.1)	14 (2.2)	3 (0.4)	4 (0.6)
Myalgia	All	90 (40.5)	103 (50.7)	48 (22.0)	44 (21.3)	250 (37.1)	271 (42.8)	122 (18.1)	109 (17.4)
	Grade 3	8 (3.6)	16 (7.9)	4 (1.8)	4 (1.9)	14 (2.1)	26 (4.1)	7 (1.0)	5 (0.8)
Shivering	All	44 (19.8)	53 (26.1)	26 (11.9)	13 (6.3)	72 (10.7)	132 (20.9)	47 (7.0)	46 (7.3)
	Grade 3	3 (1.4)	13 (6.4)	0	0	3 (0.4)	16 (2.5)	6 (0.9)	1 (0.2)
Temperature	All*	19 (8.6)	56 (27.6)	8 (3.7)	5 (2.4)	41 (6.1)	94 (14.8)	20 (3.0)	23 (3.7)
	>39†	1 (0.5)	3 (1.5)	0	0	2 (0.3)	1 (0.2)	1 (0.1)	1 (0.2)
	>39.5†	0	1 (0.5)	0	0	1 (0.1)	1 (0.2)	0	1 (0.2)

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 10.77, pp. 2429 - 2439; and Table 10.78, p. 2440
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n (%) = number/percentage of subjects reporting the symptom or the symptom of Grade 3 at least once; YOA = years of age
* Fever defined as ≥37.5°C for oral, axillary, or tympanic route or ≥38°C for rectal route.
† Temperature as assessed via any route (oral, axillary, rectal, or tympanic)

Reviewer comment: *With the exception of gastrointestinal symptoms, any grade and Grade 3 solicited general symptoms were reported in greater proportion of subjects in the younger age stratum compared to the older age stratum in the post-autoHCT population. A similar trend was seen in the immunocompetent older adult population in the original BLA. Overall by subject, Grade 3 events reported by ≥5% of HZ/su subjects after any dose were fatigue (12.1%), myalgia (9.9%) and shivering (7.1%) in the 18 – 49 YOA group and fatigue (5.8%) and myalgia (5.0%) in the ≥50 YOA group.*

Although not shown here, in both age strata, reports of any and Grade 3 headache, myalgia, and shivering increased following dose 2 compared to dose 1 of HZ/su. For the 18 – 49 YOA stratum, grade 3 fatigue increased following dose 2 compared to dose 1 and for the ≥50 YOA stratum, any and grade 3 fatigue increased following dose 2 compared to dose 1. For both age strata, any fever increased following dose 2 compared to dose 1. A notable increase in any fever was observed in subjects 18 – 49 YOA following dose 2 compared to dose 1 of HZ/su (8.6% after dose 1; 27.6% after dose 2). High fever (>39°C) was infrequent in both strata after any dose. Fever is a pertinent finding in an IC population, who may have a low threshold for initiating investigations to determine cause and empiric therapy.

The Applicant presented solicited general symptoms by underlying diagnosis (MM and 'other diagnoses'). Proportions of subjects reporting solicited general symptoms were comparable between the two strata and trends were similar to that presented for the overall study population.

Overall per dose, the mean (median) duration of fatigue, gastrointestinal (GI) symptoms, headache, myalgia, shivering and fever reported after HZ/su administration was 10.4 (3.0), 7.1 (2.0), 3.0 (2.0), 5.3 (3.0), 2.5 (1.0), and 2.5 (1.0) days, respectively. There were no notable differences in median duration of solicited general symptoms following dose 1 and dose 2.

Reviewer comment: *A majority of solicited general symptoms were of limited duration. Some reports of extended duration of solicited general symptoms may be more reflective of the post-autoHCT population, not vaccine related symptoms, as they were reported in both the HZ/su and the placebo groups.*

<u>Unsolicited Adverse Events</u>
Unsolicited AEs were recorded by all subjects on a diary card for 30 days (Days 0 – 29) after each vaccination.

Overall by subject, 39.0% and 38.2% of subjects in the TVC of the HZ/su and placebo groups, respectively, reported at least one unsolicited (serious or non-serious) AE in the 30-day post-vaccination period. The most frequently reported unsolicited AEs by Preferred Term (PT) in the HZ/su group were upper respiratory tract infection (28 subjects, 3.0% in the HZ/su and 30 subjects, 3.2% in the placebo groups), neutropenia (24 subjects, 2.6% in the HZ/su and 25 subjects, 2.7% in the placebo groups), viral upper respiratory tract infection (23 subjects, 2.5% in the HZ/su and 30 subjects, 3.3% in the placebo groups), and cough (22 subjects, 2.4% in the HZ/su and 14 subjects, 1.5% in the placebo groups). The most frequently reported unsolicited AEs by PT in the placebo group were the above AEs, as well as peripheral edema (11 subjects, 1.2% in the HZ/su and 18 subjects, 2.0%in the placebo groups).

Reviewer comment: *Overall unsolicited adverse events occurring in the month after vaccination were balanced between treatment groups. As HZ-related complications were recorded as non-serious or serious AEs, a reviewer generated analysis of non-HZ-related*

unsolicited AEs was performed and showed similar results as the analysis above as only three subjects reported unsolicited HZ-related AEs within the 30-day post-vaccination period.

Although numbers and proportions of subjects with events are small, the following numerical imbalances with more subjects reporting events in the HZ/su group compared to placebo (at least 1% in the HZ/su group and 1.5 times the proportion reporting in the placebo group) were noted: pneumonia as evaluated by the SMQ *Infective pneumonia* (17 subjects, 1.8% in the HZ/su and 10 subjects, 1.1% in the placebo groups), cough (22 subjects, 2.4% in the HZ/su and 14 subjects, 1.5% in the placebo groups), pyrexia (14 subjects, 1.5% in the HZ/su and 9 subjects, 1.0% in the placebo groups), and influenza-like illness (ILI, 12 subjects, 1.3% in the HZ/su and 6 subjects, 0.7% in the placebo groups).

Reviewer comment: *A majority of the AEs of Infective pneumonia were SAEs. Please see the discussion in section 6.1.12.4. ILI may be causally related, a surrogate for post-vaccination reactogenicity with potentially overlapping signs and symptoms (fatigue, myalgia, fever). Supporting this possibility, 9 of 12 events in the HZ/su group and 1 of 6 events in the placebo group were reported in the week following vaccination. ILI was reported by more subjects in the ≥50 YOA group compared to the 18 – 49 YOA group in the week following vaccination.*

There were also numerical imbalances in the System Organ Class (SOC) Vascular disorders (12 subjects, 1.3% in the HZ/su and 4 subjects, 0.4% in the placebo groups), Nervous system disorders (38 subjects, 4.1% in the HZ/su and 25 subjects, 2.7% in the placebo groups), and Eye disorders (10 subjects, 1.1% in the HZ/su and 4 subjects, 0.4% in the placebo groups). Imbalance in vascular disorders SOC was due to imbalances in PTs in the higher level term (HLT) of Vascular hypotensive disorders (PTs of hypotension and orthostatic hypotension) and PTs in the higher level group term (HLGT) Embolism and thrombosis. Two events of Hypotension, both in the HZ/su group, occurred on the day of dose 2 and neither was assessed as serious or related by the investigator. The other two events were more than three weeks after a vaccination and also unrelated. Regarding Embolisms and thrombosis, an analysis of the Narrow SMQ *Embolic and thrombotic events* showed that 4 subjects in the HZ/su group and 2 subjects in the placebo group reported such AEs. In the HZ/su group, two subjects reported deep vein thrombosis (DVT), day 1 and day 28 after dose 1, and one subject each reported Thrombophlebitis 7 days after dose 2 and Embolism 9 days after dose 2. The DVT reported the day after dose 1 was serious; this subject received the second dose of HZ/su without incident. The other three events in the HZ/su group were not serious. In the placebo group, one subject each reported Venous thrombosis 18 days after dose 2 and retinal vein occlusion 13 days after dose 2. None of the Embolic and thrombotic events were assessed as related by investigators. All events, except the venous thrombosis in the placebo group, occurred in subjects ≥50 YOA with multiple myeloma. The imbalance in eye disorders is due in part to conjunctival disorders (6 subjects, 0.7% in the HZ/su and 1 subject, 0.1% in the placebo groups).

Reviewer comment: *There is a small numerical imbalance in thrombotic and embolic events following vaccination (4:2) and no imbalance in serious thromboembolic events. This imbalance is not clearly attributable to HZ/su in this study in a population, which may be at increased risk for DVT. Imbalances in Nervous system disorders were due to a variety of PTs and did not follow a pattern that appeared to be clinically significant. Conjunctival disorders included seasonal allergy, conjunctivitis, and dry eye, and are not anticipated to be related to the investigational product.*

At least one Grade 3 non-serious unsolicited AE was reported by 28 (3.0%) subjects in the HZ/su group and 22 (2.4%) subjects in the placebo group within 30 days post-vaccination. The

most frequently reported Grade 3 non-serious unsolicited AEs in the HZ/su group were neutropenia (10 subjects, 1.1% in the HZ/su and 4 subjects, 0.4% in the placebo groups) and neutrophil count decreased (3 subjects, 0.3% in the HZ/su and 0 subjects in the placebo groups).The total number of subjects reporting at least one Grade 3 non-serious unsolicited AE in the sub-SMQ *Hematopoietic leukopenias*, containing these PTs, was 13 subjects (1.4%) in the HZ/su and 4 subjects (0.4%) in the placebo groups. The most frequently reported Grade 3 non-serious unsolicited AEs in the placebo group were neutropenia (see above) and diarrhea (2 subjects, 0.2% in the HZ/su and 4 subjects, 0.4% in the placebo groups). A majority of subjects in both vaccine groups with Grade 3 neutropenia had diagnoses other than multiple myeloma, in particular non-Hodgkin B cell lymphoma.

Overall by subject, 31 (3.4%) subjects in the HZ/su group and 23 (2.5%) subjects in the placebo group reported at least one unsolicited AE within the 30-day post-vaccination period assessed by the investigator as related to vaccination. The most frequent unsolicited AE with causal relationship to vaccination as per investigator assessment in both the HZ/su and placebo groups was neutropenia (5 subjects, 0.5% in the HZ/su and 3 subjects, 0.3% in the placebo groups). ILI was reported as frequently in the HZ/su group (5 subjects, 0.5% in the HZ/su and 0 subjects in the placebo groups). Of note, there were five subjects in the HZ/su group with a rash assessed as related (PTs: rash, rash generalized, rash macular, injection site rash) and none in the placebo group. One subject reported a grade 2 dyspnea on the day of vaccination, which was medically attended, treated with albuterol, resolved the same day, and assessed as related by the investigator.

Six HZ/su recipients (0.7%) and five placebo recipients (0.5%) reported AEs assessed as related that were also Grade 3 and non-serious. These events in the HZ/su group were: Four subjects with Neutropenia, two of these subjects reported one additional Grade 3 AE assessed as related (febrile neutropenia or bone marrow failure); one subject with injection site pain and one subject with ILI. Please see section 6.1.12.4 for a description of an SAE of neutropenia (not included here) assessed as related. All three AEs of neutropenia assessed by investigators as related in subjects in the placebo group were also Grade 3.

The grade 3, related event of febrile neutropenia occurred in a 21 YOA man who received an autoHCT for non-Hodgkin B cell lymphoma one day after dose 2, resolving one day later. The same subject reported Grade 3, related neutropenia 4 days post-dose 2, treated with filgrastim, and resolved 28 days later. His only other medication per the datasets was trimethoprim/sulfamethoxazole. The subject with bone marrow failure was a 58 YOA woman with non-Hodgkin B cell lymphoma who received carmustine, etoposide, cytarabine, and melphalan followed by autoHCT 64 days prior to the first dose of HZ/su. She reported mild rhinitis 7 days after dose 1 and severe (Grade 3) neutropenia 19 days after dose 1 (assessed as related), which was ongoing at the time of dose 2, 33 days after dose 1. The subject then reported severe bone marrow failure one day after dose 2, which was not serious and assessed as related. She was treated with folic acid (started at the time of neutropenia) and Lenograstim (a granulocyte colony stimulating factor added 7 days after bone marrow failure began). The neutropenia was recorded as resolved 43 days after it began and the bone marrow failure resolved 252 days after it began, with no additional AEs reported for this subject.

Reviewer comment: *Unsolicited AEs with a PT of neutropenia and with a PT in the sub-SMQ* Hematopoietic leukopenias *(36 subjects, 3.9% in the HZ/su and 30 subjects, 3.3% in the placebo groups) of any grade were balanced between treatment groups. Grade 3 AEs of neutropenia were uncommon and were reported more frequently in the HZ/su group. A similar number of subjects in each vaccination group reported Grade 3 neutropenia that was assessed*

by investigators as related. SAEs with PTs in the sub-SMQ of Hematopoietic leukopenias *through 30 days after the last vaccination were also balanced between treatment groups, making this difference in grade 3 nonserious events less likely to be clinically significant in this population.*

There were no additional events of bone marrow failure identified in the datasets for Zoster-002. Furthermore, CBER analysis showed that for the SMQs in which this PT is included (Agranulocytosis, Hematopoietic cytopenias affecting more than one type of blood cell, and the Broad SMQ Myelodysplastic syndrome) there were no differences unfavorable to HZ/su in all unsolicited AEs and SAEs at all time points examined in Zoster-002.

Unsolicited AEs by age and underlying disease: In the 18 – 49 YOA group, unsolicited AEs (serious and non-serious) in the 30-day period following vaccination were reported by 86 subjects (37.4%) in the HZ/su group compared to 72 subjects (31.4%) in the placebo group. Within this younger age stratum, both serious and non-serious AEs were reported by slightly more subjects in the HZ/su group compared to the placebo group. In subjects 18 – 49 YOA in both vaccination groups, the most frequently reported nonserious PT was upper respiratory tract infection (9 subjects, 3.9% in the HZ/su and 8 subjects, 3.5% in the placebo groups). In the 18 – 49 YOA group, Grade 3 non-serious unsolicited AEs were reported by 8 subjects (3.5%) in the HZ/su group compared to 4 subjects (1.7%) in the placebo group. In the 18 – 49 YOA, unsolicited AEs assessed as related were reported by 12 subjects (5.2%) following HZ/su and 4 subjects (1.7%) following placebo. For the ≥50 YOA group, a similar proportion of subjects reported unsolicited AEs, Grade 3 unsolicited AEs, and unsolicited AEs assessed as related in the 30-day period following HZ/su compared to following placebo.

Reviewer comment: *More 18 – 49 YOA subjects reported unsolicited AEs, grade 3 non-serious unsolicited AEs, and related AEs in the HZ/su group compared to the placebo group. More subjects in the 18 – 49 YOA in the HZ/su group also reported AEs that were medically attended and SAEs. Please see the discussion below regarding those events. With regard to nonserious unsolicited AEs of any grade, in this age group, a variety of events contributed to the imbalance including in the sub-SMQ* Hematologic leukopenias *(8 subjects in the HZ/su and 4 subjects in the placebo groups), and the PTs of cough or productive cough (7 subjects in the HZ/su and 3 subjects in the placebo group), pyrexia or body temperature increased (6 subjects in the HZ/su and 1 subject in the placebo groups), diarrhea (4 subjects in the HZ/su and 0 subjects in the placebo groups), and PTs of injection site reactions (4 subjects in the HZ/su and 1 subject in the placebo groups). Five of the eight 18 – 49 YOA subjects with Grade 3 nonserious AEs in the HZ/su group were neutropenia, neutrophil count decreased, or febrile neutropenia. No subjects 18 – 49 YOA in the placebo group reported a grade 3 non-serious neutropenia. Only one subject with these events, a subject with febrile neutropenia and neutropenia (see above), had these Grade 3 events assessed as related. This small imbalance in grade 3 neutropenia was noted in subjects 18 – 49 YOA as well as ≥50 YOA.*

Although no differences were noted in the overall proportions of subjects ≥50 years of age reporting non-serious unsolicited AEs, there was an imbalance in the SOC Nervous system disorders with 36 subjects (5.2%) in the HZ/su and 20 (2.9%) in the placebo groups reporting such events. A variety of PTs were reported in this SOC, with the most notable difference being in the HLT of Paraesthesias and dysaesthesias (9 subjects in the HZ/su and 3 subjects in the placebo groups). Other small between-group differences in subjects ≥50 YOA included the SMQ Embolic and thrombotic events (3 subjects, 0.4% in the HZ/su and 0 subjects in the Placebo groups, see discussion of these events above), the HLT of Cough and associated symptoms (20 subjects, 2.9% in the HZ/su and 12 subjects, 1.7% in the placebo groups), and the sub-

SMQ Hearing impairment, including deafness, tinnitus, and hypoacusis (4 subjects, 0.6% in the HZ/su, all mild to moderate and unrelated per investigators, and 0 subjects in the placebo groups).

In subjects with multiple myeloma, unsolicited AEs (serious and non-serious) in the 30-day period following vaccination were reported by 175 subjects (35.7%) in the HZ/su group compared to 192 subjects (38.9%) in the placebo group. In subjects in the 'other diseases' stratum, unsolicited AEs (serious and non-serious) in the 30-day period following vaccination were reported by 185 subjects (42.8%) in the HZ/su group compared to 161 subjects (37.4%) in the placebo group.

Reviewer comment: *In subjects with diagnoses other than multiple myeloma, more subjects in the HZ/su group reported unsolicited adverse events within the 30-day post-vaccination period compared to the placebo group. Differences occurred in a variety of SOCs, and no clinically significant pattern was identified.*

Medically Attended Adverse Events (MAAEs)
For each unsolicited AE, whether the AE was medically attended, defined as a hospitalization, emergency room visit or a visit to or from medical personnel (physician) for any reason, was collected and recorded on the eCRF. Therefore, medically attended AEs were analyzed for the reporting period for unsolicited AEs, the 30-day post-vaccination period following each vaccination.

Overall, 221 (24.0%) subjects in the HZ/su group and 192 (20.8%) subjects in the placebo group reported at least one unsolicited AE with medically attended visit within 30 days post-vaccination. The SOCs with the highest proportions of subjects reporting events were Infections and infestations (with 8.1% and 9.3% of HZ/su and placebo recipients reporting events, respectively) and the Neoplasms, benign, malignant and unspecified (with 3.5% and 3.6% of HZ/su and placebo recipients reporting events, respectively). The most frequently reported MAAEs in the HZ/su group by PT were neutropenia (1.6% of HZ/su and 1.5% of placebo group subjects), pneumonia (1.4% HZ/su and 0.7% placebo group subjects), upper respiratory tract infection (1.3% of HZ/su and 2.1% of placebo group subjects), and viral upper respiratory tract infection (1.1% of HZ/su and 1.4% of placebo group subjects). The most frequently reported MAAEs in the placebo group were upper respiratory tract infection (see above), neutropenia (see above), viral upper respiratory tract infection (see above), and plasma cell myeloma (0.8% of HZ/su and 1.1% of placebo group subjects).

Reviewer comment: *No patterns of imbalance were observed between treatment groups except those noted elsewhere (see SAEs of pneumonia below).*

More subjects in the 18 – 49 YOA group reported unsolicited AEs that were medically attended in the 30 days following HZ/su (23.9%) compared to following placebo (17.0%). Similar to the small differences in this age stratum between treatment groups previously noted, differences in hematopoietic leukopenias and infective pneumonia were observed in medically attended AEs.

In subjects with multiple myeloma, unsolicited AEs (serious and non-serious) that were medically attended in the 30-day post-vaccination period were reported by 99 subjects (20.2%) in the HZ/su group compared to 97 subjects (19.7%) in the placebo group. In subjects with other diseases, unsolicited AEs (serious and non-serious) in the 30-day post-vaccination period were reported by 122 subjects (28.2%) in the HZ/su group compared to 95 subjects (22.0%) in the placebo group.

Reviewer comment: *As above, more subjects in the HZ/su group with diagnoses other than multiple myeloma reported unsolicited AEs that were medically attended within the 30-day post-vaccination period, but no pattern or clusters of events were observed.*

6.1.12.3 Deaths

A summary of subjects in the TVC with fatal SAEs (who died) during select time periods by treatment group is below.

Table 28. Subjects who died during selected time periods, Zoster-002 (TVC)

	HZ/su N=922 n (%)	**Placebo N=924 n (%)**
Subjects who died Days 0 – 29 post-vaccination	1 (0.1)	3 (0.3)
Subjects with fatal SAE reported Day 0 – Month 13	51 (5.5)	49 (5.3)
Subjects with fatal SAE reported (whole post-vaccination period)	118 (12.8)	124* (13.4)

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 10.77, pp. 2429 - 2439
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n (%) = number/percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
* One placebo group subject ((b) (6)) is included in deaths reported during the whole post-vaccination period, but the exact timing of the death is unknown; the fatal event of non-Hodgkin B cell lymphoma started 69 days after dose 2.

Reviewer comment: *There were also no clinically significant differences between treatment groups in the proportions of subjects with the onset of fatal SAEs by the above time periods.*

Fatal SAEs with death within 30 days post-vaccination: One subject in the HZ/su group and three subjects in the placebo group died within 30 days following vaccination. The causes of death by PT were cardiac failure in the Hz/su group and pneumonia in two subjects and sepsis and plasma cell leukemia in the third subject in the placebo group. The death in the HZ/su group occurred in a 55 YO man without a history of cardiac disease, who received carmustine, etoposide, cytarabine, cyclophosphamide, mesna, and a standard autoHCT for non-Hodgkin B cell lymphoma 65 days prior to dose 1 of HZ/su who presented to the emergency room (b) (6) days after receiving dose 1 with “general deterioration”, dyspnea, and intermittent confusion. He was afebrile, tachycardic, with a reduced ejection fraction, and elevated C-reactive protein (CRP), creatinine, and liver enzymes. Empiric antibiotics were initiated for a possible respiratory infection. His status declined rapidly with hypoxia, hypoglycemia, and hypotension noted prior to his death. No other AEs were recorded, and the diary card was not collected. The cause of death was assessed as PT = Cardiac failure of unknown cause. The investigator assessed the event as not related to investigational product and possibly due to his underlying disease.

Reviewer comment: *The underlying cause of death is unclear. Although the death is temporally related to vaccination, the subject had other potential etiologies, including his NHBCL and toxicity due to his conditioning regimen.*

Fatal SAEs with death within one year post-vaccination: During this period, 51 (5.5%) and 49 (5.3%) subjects died in the HZ/su and placebo groups, respectively. By PT, the most frequently reported fatal events during this time were plasma cell myeloma (16 subjects, 1.7% in the HZ/su and 13 subjects, 1.4% in the placebo groups), diffuse large B-cell lymphoma (6 subjects, 0.7% in the HZ/su and 3 subjects, 0.3% in the placebo group), lymphoma (5 subjects, 0.5% in the HZ/su and 6 subjects, 0.6% in the placebo groups), and sepsis (4 subjects, 0.4% each in the HZ/su and placebo groups) in the HZ/su group and plasma cell myeloma, lymphoma, sepsis, and pneumonia (2 subjects, 0.2% in the HZ/su and 4 subjects, 0.4% in the placebo groups) in

the placebo group. The greatest proportions of subjects experienced fatal events in SOCs Neoplasms benign, malignant and unspecified and Infections and infestations, with the proportions of subjects reporting events in these SOCs similar between treatment groups. Comparative analysis indicated that there were no clinically significant differences between treatment groups in the proportions of subjects who died by PT and SMQ.

Fatal SAEs during the whole study period: During the whole post-vaccination period, 118 (12.8%) and 124 (13.4%) subjects died in the HZ/su and placebo groups, respectively. By PT, the most frequently reported fatal events during the entire study period were plasma cell myeloma (4.7% of HZ/su and 4.7% of placebo group subjects), sepsis (1.1% of HZ/su and 0.4% of placebo group subjects), and diffuse large B-cell lymphoma (0.9% of HZ/su and 0.4% placebo group subjects) in the HZ/su group and plasma cell myeloma (see above), pneumonia (0.4% of HZ/su and 1.2% of placebo group subjects), and lymphoma (0.8% of HZ/su and 1.1% of placebo Group subjects) in the placebo group. The greatest proportions of subjects experienced fatal events in the SOCs of Neoplasms benign, malignant and unspecified and Infections and infestations, with the proportions of subjects reporting events in these SOCs comparable between treatment groups.

Some differences were noted between vaccination groups in proportions of subjects who died throughout the entire study period in the PT (see above) and SMQ *Sepsis* (18 subjects, 2.0% in the HZ/su and 9 subjects, 1.0% in the placebo group) and in the SOC Renal and urinary disorders, attributable to the SMQ *Acute renal failure* (9 subjects, 1.0% in the HZ/su group and 3 subjects, 0.3% in the placebo group). Within 365 days of the last study vaccination, fatal SAEs due to these SMQs were similar between groups (sepsis: 6 subjects,0.7% in the HZ/su group and 4 subjects, 0.4% in the placebo group; acute renal failure: 3 subjects, 0.3% in the HZ/su group and 2 subjects, 0.2% in the placebo group). In addition, there were four subjects in the HZ/su group (0.4%) with a fatal SAE during the entire study in the SMQ *Embolic and thrombotic events*, arterial (including PTs of myocardial infarctions, mesenteric artery thrombosis, and thrombotic microangiopathy), and 0 subjects in the placebo group. Within 365 days following the last vaccination, no subjects in either group had a fatal SAE in the SMQ *Embolic and thrombotic events, arterial*.

Reviewer comment: *The differences in these events occurring more than one year following the last study vaccination and the fact that (fatal and nonfatal) SAEs up to 30 days and 365 days post-last vaccination were reported in similar or higher proportions of subjects in the placebo group, suggests they are more likely due to chance. (The SMQ analysis was done on Zoster-002 from the ISS datasets using MedDRA, version 22.1, which has an SMQ of Sepsis).*

Related fatal SAEs: No fatal SAEs were assessed as related to vaccination by the investigator throughout the entire study period.

Fatal SAEs by age group and disease: The proportions of subjects who died in each age group increased with advancing age. During the one-year post-vaccination period, a numerically higher proportion of subjects 18 – 49 YOA in the HZ/su group died (10 subjects, 4.3%) compared to the placebo group (6 subjects, 2.6%). At other time points, the proportions who died within each age group were comparable between treatment groups. The proportion of subjects who died at the time points evaluated by underlying disease was comparable between treatment groups.

Reviewer comment: *All but one of the 18 – 49 YOA who died within one year following vaccination had a relapse, progression, or another malignancy. The subject who died from a*

cause other than malignancy was a 48 YOA woman post-autoHCT for Hodgkin lymphoma who died from Acinetobacter baumannii *sepsis 42 days after dose 2 of HZ/su. The slight difference between treatment groups in the proportion of subjects who died within one year of vaccination in the 18 – 49 YOA group is unlikely to be clinically significant.*

6.1.12.4 Nonfatal Serious Adverse Events

The Applicant included both fatal and non-fatal SAEs in their tabulations of SAEs. All SAEs were monitored through one-year post-vaccination. A summary of SAEs occurring up to 30 days and 365 days following the last vaccination the subject received is below.

Table 29. Summary of SAEs up to 30 days and 365 days post-last vaccination, Zoster-002 (TVC)

	HZ/su N=922 n (%)	Placebo N=924 n (%)
Subjects with at least one SAE reported up to 30 days post-last vaccination	68 (7.4)	66 (7.1)
Subjects with at least one SAE reported up to 365 days post-last vaccination	263 (28.5)	241 (26.1)

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 10.33, pp. 2368 – 2371; and Table 10.35, pp. 2373 – 2383
SAE = serious adverse event; TVC = total vaccinated cohort; N = number of subjects with at least one administered dose; n (%) = number/percentage reporting the symptom

Reviewer comment: *Overall by subject, the proportion of subjects who reported SAEs within one month and one year of last vaccination were similar between treatment groups.*

Up to 30 days post-last vaccination, the most frequently reported SAEs by PT in both the HZ/su and placebo groups were pneumonia (12 subjects, 1.3% in the HZ/su and 7 subjects, 0.8% in the placebo group) and plasma cell myeloma (6 subjects, 0.7% in the HZ/su and 9 subjects, 1.0% in the placebo group). The SOCs with the greatest proportions of subjects reporting SAEs were Neoplasms and Infections and infestations, with similar proportions of subjects reporting SAEs within these SOCs in both treatment groups. The sub-SMQ of *Hematologic malignant tumors*, containing the PT plasma cell myeloma (23 subjects, 2.5% in the HZ/su and 28 subjects, 3.0% in the placebo groups) and the SMQ of *Infective pneumonia*, containing the PT pneumonia, (15 subjects, 1.6% in the HZ/su and 10 subjects, 1.1% in the placebo groups) were among the most frequently reported SMQs. The SMQ of *Malignant lymphomas* (16 subjects, 1.7% in the HZ/su and 15 subjects, 1.6% in the placebo groups) was another frequently reported SMQ. Two subjects reported SAEs in the SMQ *Interstitial lung disease*, one of which was diagnosed as pneumonitis by PT with the narrative describing a computed tomography scan showing “pulmonary emphysema and pulmonary superinfection of the two bases;” this may be suggestive of a pneumonia. Please see section 8.4.8 describing the serious pIMD in the SMQ *Interstitial lung disease*.

Reviewer comment: *Up to 30 days post-last vaccination, a potentially clinically significant difference between treatment groups was observed in SAEs of infective pneumonia. Although not a pre-specified analysis, the reviewer analyzed SAEs reported within two weeks of vaccination, which showed a numerical imbalance with 36 subjects (3.9%) in the HZ/su group and 21 subjects (2.3%) in the placebo group reporting SAEs. At two weeks post-vaccination a numerical imbalance is noted in the SOC* Infections and Infestations *(12 subjects, 1.3% in the HZ/su and 5 subjects, 0.5% in the placebo groups), driven by the numerical imbalance in the SMQ of Infective PNA (9 subjects, 1.0% in the HZ/su and 2 subjects, 0.2% in the placebo group). Theoretical mechanisms for a relationship with vaccine could include a post-vaccination*

inflammatory response (fever, fatigue, myalgia) increasing diagnoses of pneumonia (though day of onset in the HZ/su group is spread throughout the two weeks post-vaccination, not clustered in the first week post-vaccination) or an increased susceptibility to infection due to an immune response directed toward HZ. Please also see the discussion on pneumonia and pneumonitis up to 30 days following vaccination in the pooled safety data, section 8.4.2.

In the one-year post-vaccination period, the most frequently reported SAEs by PT in both the HZ/su and placebo groups were plasma cell myeloma (59 subjects, 6.4% in the HZ/su and 41 subjects, 4.4% in the placebo group) and pneumonia (42 subjects, 4.6% in the HZ/su and 30 subjects, 3.3% in the placebo group). The SOCs with the greatest proportions of subjects reporting SAEs were Neoplasms, benign, malignant, and unspecified (14.5% in the HZ/su and 11.8% in the placebo groups) and Infections and infestations (11.8% in the HZ/su and 11.7% in the placebo groups). The SMQs *Malignancies, hematologic malignant tumors*, containing the PT plasma cell myeloma (125 subjects, 13.6% in the HZ/su and 103 subjects 11.2% in the placebo groups) and Infective pneumonia, containing the PT pneumonia, (53 subjects, 5.8% in the HZ/su and 41 subjects, 4.1% in the placebo groups) were among the most frequently reported SMQs. 'Malignant lymphomas,' containing events which are also included under the SMQ *Hematologic malignancies* (59 subjects, 6.4% in the HZ/su and 51 subjects, 5.5% in the placebo groups) was another frequently reported SMQ.

Reviewer comment: *The numerical differences in SAEs with a PT in the SMQ Infective pneumonia diminished over time. More subjects died due to pneumonia (had a fatal SAE with a PT in the SMQ Infective pneumonia) up to 30 days and 365 days post-last vaccination in the placebo group compared to the HZ/su group, although the number of these events are small (2 subjects in the placebo group at 30 days, and 2 subjects in the HZ/su and 4 subjects in the placebo groups at 365 days). The numerical differences in hematologic malignancies are small and unlikely to be clinically significant. Please also see section 6.1.12.5 on Adverse events of Special Interest (AESIs) for relapse and progression.*

As HZ-related SAEs were recorded as SAEs and included in the above SAE summaries, creating the potential to mask a safety concern of an effective vaccine, the clinical reviewer assessed non-HZ SAEs. Up to 30 days post-last vaccination, 68 HZ/su recipients (7.4%) and 65 (7.0%) placebo recipients reported non-HZ-related SAEs. Up to 365 days post-last vaccination, 262 HZ/su recipients (28.4%) and 235 placebo recipients (25.4%) reported non-HZ-related SAEs.

Reviewer comment: *The results of the non-HZ-related SAE analysis are similar to the analysis of all SAEs.*

<u>SAEs by age and underlying disease:</u>
The proportions of subjects in each age stratum reporting at least one SAE during select time periods post-vaccination is below.

Table 30. Subjects reporting the occurrence of SAEs up to 30 days and 365 days post-last vaccination by age strata, Zoster-002 (TVC)

	HZ/su 18 – 49 YOA N=230 n (%)	Placebo 18 – 49 YOA N=229 n (%)	HZ/su ≥50 YOA N=692 n (%)	Placebo ≥50 YOA N=695 n (%)
Subjects with at least one SAE reported up to 30 days post-last vaccination	18 (7.8)	13 (5.7)	50 (7.2)	53 (7.6)
Subjects with at least one SAE reported up to 365 days post-last vaccination	47 (20.4)	50 (21.8)	216 (31.2)	191 (27.5)

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 10.106, pp. 2525 – 2528, and Table 10.108, pp. 2530 – 2541
SAE = serious adverse event; TVC = total vaccinated cohort; YOA = years of age; N = number of subjects with at least one administered dose; n (%) = number/percentage reporting the symptom

Reviewer comment: *More subjects in the 18 – 49 YOA stratum in the HZ/su group reported SAEs with PTs in the SMQ of Infective pneumonia (5 subjects in the HZ/su and 1 subject in the placebo groups) and with the PT of Hodgkin's disease (4 subjects in the HZ/su and 1 subject in the placebo groups) up to 30 days post-last vaccination. All other neoplasms combined were reported at similar frequency in this age group. The numbers reporting SAEs in the younger age strata are small, so clinical significance is difficult to conclude.*

There was a numerical imbalance between treatment groups in the proportion of SAEs reported up to 365 days post-last vaccination in subjects with multiple myeloma (29.2% in the HZ/su and 24.3% in the placebo group), due in part to differences in the proportion of subjects reporting SAEs with the PT of plasma cell myeloma (12.0% in the HZ/su and 8.1% in the placebo group) at this time point. There were no notable differences in the proportion of subjects reporting SAEs between treatment groups in subjects with multiple myeloma up to 30 days post-last vaccination or in subjects in the other underlying diseases stratum.

Reviewer comment: *Please see the discussion below regarding relapse. It appears that the difference between treatment groups in the SAEs of plasma cell myeloma was not due to a difference in the occurrence of relapse, but a difference in reporting those relapses as serious or non-serious.*

Related SAEs: The investigators assessed one SAE in HZ/su recipients and three SAEs in placebo recipients to be causally related to vaccination up to 30 days post-last vaccination. The investigators assessed three SAEs in HZ/su recipients and four SAEs in placebo recipients to be causally related to vaccination up to 365 days post-last vaccination. After one year post-vaccination, no additional SAEs were assessed as causally related.

The related SAE in a subject in the HZ/su group reported within 30 days of the last vaccination occurred in a 41 y/o man treated with carmustine, etoposide, cytarabine, melphalan, and standard autoHCT for follicular lymphoma 61 days prior to dose 1 of HZ/su. At the time of vaccination, the subject was reported to have neutropenia and his follicular lymphoma was in remission. He received dose 1 and filgrastim 2 days later for "prevention of neutropenia." He reported diarrhea 11 days after dose 1 and moderate "worsened" neutropenia and pneumonia 13 days after dose 1, for which he was hospitalized. He was treated with filgrastim, levofloxacin, meropenem, voriconazole, and paracetamol and recovered from both SAEs 15 days later. He didn't receive dose 2 of HZ/su as the investigator considered the vaccine could have worsened the neutropenia. The remaining two SAEs assessed as related in subjects in the HZ/su group occurred >30 days post-vaccination and were pIMDs (see event descriptions in section 8.4.8).

Reviewer comment: *Although there is a temporal relationship of worsened neutropenia with vaccination, this subject had neutropenia prior to vaccination. As noted above, unsolicited AEs and SAEs of neutropenia (including PTs in the SMQ Hematopoietic leukopenias and agranulocytosis) were reported in the 30 days post-vaccination similarly between groups, though non-serious grade 3 neutropenia was more frequent in the in the HZ/su group.*

6.1.12.5 Adverse Events of Special Interest (AESI)

Potential immune-mediated diseases (pIMDs): pIMDs were collected for the one-year post-vaccination period. The number and proportion of subjects reporting pIMDs at different time points by vaccination group is below.

Table 31. Subjects reporting the occurrence of pIMDs at selected time points, Zoster-002 (TVC)

	HZ/su N=922 n (%)	Placebo N=924 n (%)
Subjects with at least one pIMD reported up to 30 days post-last vaccination	4 (0.4)	2 (0.2)
Subjects with at least one pIMD reported up to 365 days post-last vaccination	13 (1.4)	8 (0.9)

Source: Adapted from 125614/398.0, Zoster-002 CSR, Table 10.52, p. 2403; and Table 10.54, p. 2405
pIMD = potential immune-mediated disease; TVC = total vaccinated cohort; N = number of subjects with at least one administered dose; n (%) = number/percentage reporting the symptom

Up to 30 days post-last vaccination, at least one pIMD was reported in 4 subjects (0.4%) in the HZ/su and 2 subjects (0.2%) in the placebo group. Events reported in HZ/su recipients were psoriasis in two subjects, autoimmune hemolytic anemia, and interstitial lung disease. Events reported in the placebo group were spondylitis and psoriasis.

Up to 365 days post-last vaccination, 13 (1.4%) HZ/su recipients and 8 (0.9%) placebo recipients reported at least one pIMD. The most frequently reported pIMDs by PT were Psoriasis reported for 2 subjects (0.2%) in the HZ/su group and 1 subject (0.1%) in the placebo group all occurring up to 30 days following the last vaccination and noted above; and Interstitial lung disease reported for 1 subject (0.1%) in the HZ/su within and 2 (0.2%) subjects in the placebo group. The SOCs with the highest proportions of subjects in the HZ/su group reporting events was Skin and subcutaneous tissue disorders (4 subjects in the HZ/su group reporting the two pIMDs of Psoriasis, Cutaneous vasculitis, and Hypersensitivity vasculitis and one subject in the placebo group reporting Psoriasis) and Blood and lymphatic system disorders (three subjects HZ/su group reporting Autoimmune hemolytic anemia, Hemophagocytic lymphohistiocytosis, and Immune thrombocytopenic purpura and no subjects in the placebo group). No SOCs had more than two placebo recipients reporting events.

Although not pre-specified for collection, there were four pIMDs reported after the 365-day post-vaccination period – Guillain Barré syndrome, demyelinating polyneuropathy, and VIth nerve paralysis in the HZ/su group and facial paralysis in the placebo group. None of these AEs were assessed by investigators as related.

Three subjects (0.3%), all in the HZ/su group, had four pIMDs that were assessed by investigators as being causally related to investigational product. The pIMDs with causal relationship to vaccination were psoriasis; immune thrombocytopenic purpura; and arthralgia and cutaneous vasculitis occurring concurrently within the same subject.

Reviewer comment: *See section 8.4.8 for event descriptions and CBER analysis of pIMD reporting across studies.*

Relapses and progression of underlying disease: The reporting of both disease progression and relapse was done according to the investigators' medical judgment based on local medical practice. There were no clinical criteria provided for reporting of disease progression or relapse events.

Any relapse, defined as a recurrence of the underlying malignancy or disease for which the autoHCT was undertaken, was recorded, from Month 0 until study end, as an SAE or non-serious AE as appropriate, and was specifically identified by investigators as a relapse. The number and proportion of subjects reporting events of relapse at different time points by vaccination group is below.

Table 32. Subjects reporting the occurrence of relapse at selected time points, Zoster-002 (TVC)

	HZ/su **N=922 n (%)**	**Placebo N=924 n (%)**
Subjects with at least one relapse reported up to 30 days post-last vaccination	24 (2.6)	29 (3.1)
Subjects with at least one relapse reported up to 365 days post-last vaccination	145 (15.7)	149 (16.1)
Subjects with at least one relapse reported during the entire study period	239 (25.9)	253 (27.4)

Source: Adapted from 125614/398.0, CSR Table 10.58, p. 2409; and 10.54, p. 2405
TVC = total vaccinated cohort; N = number of subjects with at least one administered dose; n (%) = number/percentage reporting the symptom

Reviewer comment: *The proportions of subjects reporting events assessed as relapse were similar at the specified time points.*

Disease progression was not specifically defined in the protocol. In 125614/398.11, in response to a CBER IR, the Applicant stated that instructions were provided on how to record relapse and progression events in order to distinguish them clearly in the database. For disease progression, sites were instructed to use a derivative of the word "progression" in the verbatim term of the AE. Investigators were specifically asked to identify progression events as relapse (by not checking the "relapse" box; hence the two terms were to capture different events. The Applicant conducted a post hoc analysis of disease progression by selecting verbatim terms containing a derivative of "progression".

Over the entire study period, at least one AE of disease progression was reported in 81 (8.8%) and 82 (8.9%) subjects in the HZ/su and placebo groups, respectively.

Reviewer comment: *As progression was not specified in the protocol, collection of this outcome may not have been uniform. The distinction between relapse and progression is not clear as definitions were not pre-specified. However, the reviewer identified no events that were categorized as both. In addition, at 30 days and 365 days post-vaccination, the number of subjects reporting events identified as progression were similar between vaccination groups. These analyses support that HZ/su vaccination did not contribute to the underlying diseases.*

6.1.12.7 Dropouts and/or Discontinuations

Please see section 6.1.10.1.3 for subject disposition. Of 13 HZ/su recipients who were withdrawn from vaccination at Visit 2 for a serious or non-serious AE, two were assessed as related: a non-serious pIMD of psoriasis (see section 8.4.8) and a non-serious AE of myalgia (moderate, starting 21 days post-dose 1 and resolving 36 days later in a 56 YOA woman with Hodgkin lymphoma). Of the 11 HZ/su recipients who did not complete Visit 2 due to a serious or non-serious AE, two were assessed as related: an SAE of neutropenia in the setting of pneumonia (see section 6.1.12.4) and a non-serious AE of moderate neutropenia reported as starting day 32 post-dose 1 (resolution not recorded). Of the 11 placebo recipients who were withdrawn from vaccination at Visit 2 for a serious or non-serious AE, one was assessed as related: a nonserious AE of discoid eczema. Of the 18 placebo recipients who did not complete Visit 2 due to a serious or non-serious AE, two were assessed as related: one SAE of Toxic skin eruption reported on the day of dose 1 and resolving 7 days later, and one SAE of Constipation reported 9 days after dose 1 and resolving 2 days later.

Up to Visit 4/M13, 13.2% of subjects (12.5% in the HZ/su and 14.0% in the placebo groups) were withdrawn. This includes 8.7% (8.5% in the HZ/su and 8.8% in the placebo groups) who were withdrawn for serious or non-serious AEs. Of these AEs leading to study withdrawal, the nonserious AE of neutropenia in an HZ/su recipient and the SAE of Toxic skin eruption in a placebo recipient were the only events assessed as related. Other related events either did not lead to study withdrawal or were not considered by investigators as the reason for study withdrawal. At time points beyond Visit4/M13, the proportion of subjects withdrawing from the study and the proportion withdrawing due to AEs was similar between groups.

Reviewer comment: *A similar number of subjects in each vaccination group were withdrawn from treatment and withdrawn from the study at the time points evaluated, as well as withdrawn due to SAEs and AEs. The high withdrawal rate was anticipated in the study design.*

6.1.13 Study Summary and Conclusions

Zoster-002 a Phase 3, randomized, placebo-controlled, multi-center trial that evaluated two doses of HZ/su or placebo (1:1 randomization) administered IM at Month 0 and Month 1-2 to 1,846 adult subjects 50 – 70 days following an autoHCT. HZ VE was demonstrated in this population [68.2% (95% CI: 55.6%, 77.5%)] after an approximate median follow-up time of 21 months. HZ VE was comparable in subgroups by age (18 – 49 and ≥50 YOA), gender, race (Asian and White), and underlying disease (MM and other diseases). HZ VE could not be confirmed in some subgroups which enrolled fewer numbers of subjects – African American Heritage and American Hispanic/Latino. Approximately 20% of subjects received PAT for more than 60 days during the study and HZ VE was not demonstrated in this population in a post hoc analysis [37.8% (-42.3%, 73.4%)] that was not statistically powered to detect a difference. HZ VE was demonstrated in the overall study population in the first year after transplant, during a time when autoHCT recipients are at highest risk of HZ [76.2% (61.1%, 86.0%)].

Reactogenicity occurred in almost all subjects in this IC population. IS pain was the most commonly reported solicited local symptom and fatigue and myalgia were the most commonly reported general solicited symptoms after HZ/su administration. Grade 3 reactogenicity was not uncommon, particularly for pain, fatigue, and myalgia. Fever was reported frequently in this population (20%), but fever >39° was rare. General solicited symptoms were more frequent following the second dose than the first.

Generally, deaths, SAEs, pIMDs, and unsolicited AEs were reported at similar frequency between vaccination groups. There was a numerical imbalance in SAEs of pneumonia reported up to 30 days following dose 2, and particularly in the two weeks post-vaccination. The clinical significance of this observation in a population at greater risk of infection at baseline is unclear, but a relationship to vaccination can't be ruled out.

6.2 Trial #2

Zoster-039: "A Phase 3, randomized, observer-blind, placebo-controlled, multicenter study to assess the safety and immunogenicity of HZ/su when administered intramuscularly on a two-dose schedule to adults aged 18 years and older with hematologic malignancies."

Study dates
Study initiation date: March 1, 2013
Study completion date: January 6, 2017

6.2.1 Objectives

Co-primary objectives

- To evaluate the safety and reactogenicity following administration of HZ/su compared to placebo from the first vaccination up to 30 days post-last vaccination in subjects with hematologic malignancies, aged 18 years and older (the analysis for this objective was descriptive).
- To evaluate the VRR for anti-gE humoral immune responses at Month 2 following a two-dose administration of the HZ/su vaccine in subjects with hematologic malignancies excluding subjects with Non-Hodgkin B-cell lymphoma (NHBCL) and chronic lymphocytic leukemia (CLL).
- To evaluate anti-gE humoral immune responses at Month 2 following a two-dose administration of HZ/su, as compared to placebo in subjects with hematologic malignancies excluding subjects with NHBCL and CLL.

Select secondary objectives:

- To evaluate safety following administration of the HZ/su vaccine, compared to placebo, from the first vaccination up to 6 months post-last vaccination in at least 50% of the total vaccinated cohort (TVC) in subjects with hematologic malignancies, aged 18 years and older.
- To evaluate safety following administration of the HZ/su vaccine, as compared to placebo, from 30 days post-last vaccination until study end in subjects with hematologic malignancies, aged 18 years and older.
- To evaluate the incidence of confirmed HZ cases in subjects with hematologic malignancies, aged 18 years and older.
- To characterize anti-gE humoral immune responses at Months 0, 1, 2, and 13 within the HZ/su and placebo groups, in subjects with hematologic malignancies and by underlying disease strata.
- To characterize gE-specific CD4+ T-cell mediated immune responses at Months 0, 1, 2, and 13 within the HZ/su and placebo groups, in the CMI sub-cohort and by underlying disease strata.

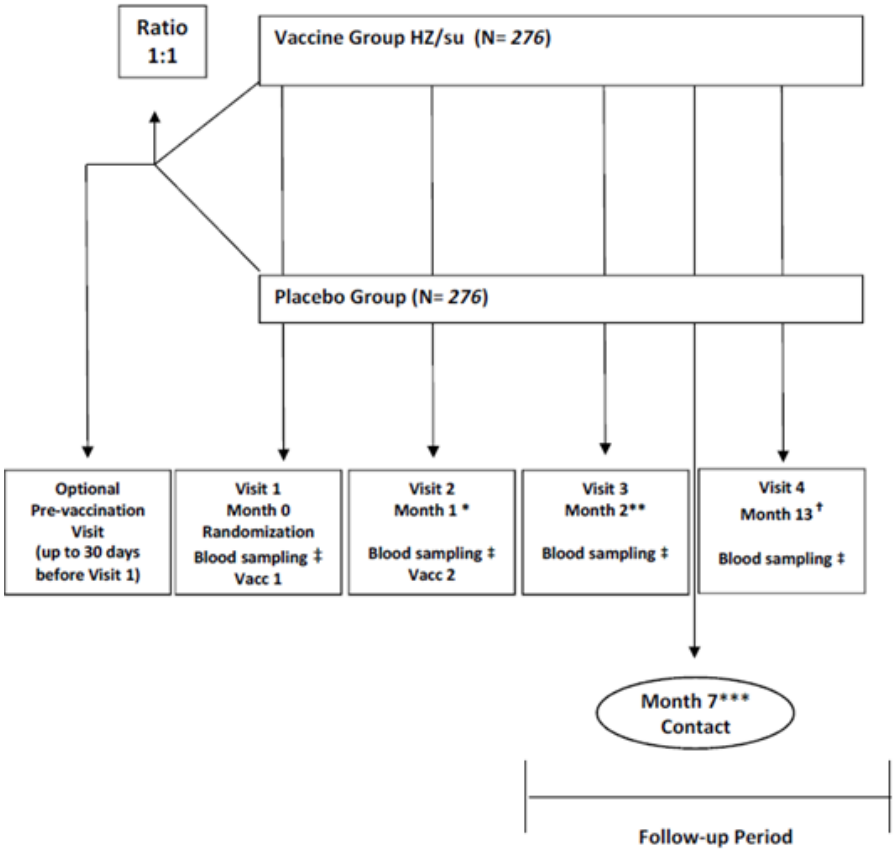
Reviewer comment*: The estimate of vaccine efficacy was not an objective of the study*.

6.2.2 Design Overview

The study was a Phase 3 randomized, placebo-controlled, observer-blind, multicenter study with a planned enrollment of 552 adult subjects ≥18 YOA (276 per treatment group) diagnosed with hematologic malignancies who were at increased risk of HZ because they were or were planned to be treated with immunosuppressive cancer treatment. Subjects were randomized 1:1 to receive two intramuscular (IM) doses of HZ/su or placebo (lyophilized sucrose cake and saline solution) one month apart (the second dose could be administered 1 – 2 months after the first dose). The randomization algorithm used a stratification factor to account for underlying disease (NHBCL 50 – 70 subjects; CLL 50 – 70 subjects; and MM and other 400 – 452 subjects). A minimization procedure accounted for the following characteristics: underlying disease (non-Hodgkin B-cell lymphoma, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin T-cell lymphoma, Hodgkin lymphoma, or other hematologic malignancies), timing of immunosuppressive cancer therapy (during – vaccination during cancer therapy course with at least 10 days between cancer therapy cycles and each vaccination; or after – vaccination after the full cancer therapy course from 10 days to 6 months after cancer therapy has ended), age (18 – 49 and ≥50 YOA), region, country, center and gender. Four study visits (two vaccination visits) and an optional pre-vaccination visit were scheduled; total study participation time per subject was approximately 13 months (12 months post-final vaccination.)

A schematic of the study design is presented below:

Figure 4. Study Design, Zoster-039



Source: 125614/398.0, Zoster-039 CSR, Section 5.1.1, p. 93
* The second dose of study vaccine/placebo was administered 1 to 2 months after the first dose.
** Month 2 (Visit 3) was to occur 1 month after the second vaccination.
*** Month 7 contact was to occur 6 months after the second vaccination.
† Month 13 (Visit 4) was to occur 12 months after the second vaccination.
‡ Blood samples were to be collected from all subjects at Visits 1 through 4.

Study product was administered with consideration given to planned cancer therapy. Study product administration was pre-specified as follows:

- If each cancer treatment was separated by ≥20 days, the first vaccination was to be planned as late as possible during that time period while still allowing 10 days before the next planned treatment
- If the cancer treatment cycle did not allow spacing of vaccination between each cancer treatment by at least 10 days, the first vaccination was to be scheduled from 10 days to 6 months after the full cancer therapy course.
- The second dose of study vaccine was to be administered 1 to 2 months after the first dose.

Reviewer comment: *The Applicant does not provide a rationale for evaluating HZ/su administered both during chemotherapy and up to 6 months following the completion of chemotherapy. It is biologically plausible that concurrent administration of cancer therapies that alter immune function could adversely impact response to vaccination. However, the study was not powered or designed to look at the timing of vaccination in relation to cancer treatment and vaccine immune response.*

6.2.3 Population

Key inclusion criteria

- Subjects 18 YOA or older who had a life expectancy ≥12 months
- Subject diagnosed with one or more hematologic malignancies prior to the first vaccination and who is receiving, is scheduled to receive, or has just received immunosuppressive cancer therapy (chemotherapy or immunotherapy) to treat the condition
- Female subjects of child-bearing potential were able to enroll if they had practiced adequate contraception (defined appropriately in the protocol) for 30 days prior to first vaccination, have a negative pregnancy test on the day of vaccination and who agreed to continue adequate contraception during the treatment period and for two months after completion of the vaccination series.

Key exclusion criteria

- Subjects receiving radiotherapy only for cancer treatment
- Subjects with chronic lymphocytic leukemia receiving only oral chemotherapy
- Planned HCT during the study period (if HCT occurred prior to enrollment, study product should be administered a minimum of 50 days after the transplant procedure)
- HIV infection by clinical history
- Previous vaccination against HZ or varicella within the 12 months preceding the first dose of study product
- Occurrence of a varicella or HZ episode by clinical history within 12 months prior to the first dose of study product
- Pregnant or lactating female or female planning to become pregnant or discontinue contraception within 2 months after the last dose of study product
- Use of investigational or non-registered product other than the study product within 30 days preceding the first dose of study product or planned use during the study period
- Administration of a live vaccine within the period 30 days prior to the first dose of study product to 30 days after the last dose of study product or administration of a non-replicating vaccine within 8 days prior to or within 14 days after either dose of study product

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study products were as follows:

Table 33. Vaccine and comparator composition/dose/lot number, Zoster-039

Treatment Name	Component Name*	Formulation	Presentation	Lot Numbers
HZ/su	VZV gE	50 µg gE per 0.5 mL of reconstituted vaccine	Lyophilized pellet in a monodose vial	DVZVA007B, DVZVA008A, DVZVA009A, DVZVA008B
HZ/su	$AS01_B$	MPL, QS21 and liposome (50 µg MPL and 50 µg QS21) per 0.5 mL of reconstituted vaccine	Liquid in a monodose vial	DA01A050A, DA01A055A, DA01A056A, DA01A055B
Placebo	Lyophilized sucrose cake	(b) (4) sucrose per 0.5 mL of reconstituted placebo	Lyophilized pellet in a monodose vial	PVZVA003A, PVZVA005A
Placebo	Saline (NaCl) solution for reconstitution	(b) (4) NaCl solution (water for injection)	Liquid in a monodose vial	DD02A009A, DD02A011A

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 7, p. 106
VZV = Varicella Zoster Virus; gE = recombinant purified glycoprotein E; $AS01_B$ = Adjuvant System $AS01_B$; NaCl = sodium chloride; MPL =3-O-desacyl monophosphoryl lipid A; QS21 = *Quillaja saponaria* Molina, fraction 21

6.2.5 Directions for Use

The vaccine or placebo was reconstituted and kept at room temperature prior to administration, which was to occur within 6 hours. The HZ/su vaccine and placebo were administered IM to the deltoid region of the non-dominant arm. Following product administration, subjects were observed for at least 30 minutes with appropriate medical treatment available in the case of an anaphylactic reaction.

The second dose of HZ/su was to be administered within 30 to 60 days after the first dose.

6.2.6 Sites and Centers

There were 77 centers in 21 countries in 5 regions. The majority of subjects (62.5%) were from Europe and South Africa.

Table 34. Number of subjects with centers by country and region, Zoster-039 (TVC)

Country	Region	Centers	HZ/su n (%) Total =283	Placebo n (%) Total =279
All countries	**Asia Pacific**	**All centers**	**78 (27.6)**	**76 (27.2)**
Australia	Asia Pacific	200417, 200904, 200905, 200906	13 (4.6)	14 (5.0)
Korea, Republic of	Asia Pacific	105948, 105949, 105951, 105952, 200122, 200126, 200131, 209434	44 (15.5)	45 (16.1)
New Zealand	Asia Pacific	200418, 200907	5 (1.8)	4 (1.4)
Singapore	Asia Pacific	200728	1 (0.4)	0 (0)
Taiwan	Asia Pacific	200337, 200338, 200560, 200561	15 (5.3)	13 (4.7)
All countries	**Europe**	**All centers**	**130 (45.9)**	**128 (45.9)**
Belgium	Europe	107841, 107846, 107858, 107872	15 (5.3)	15 (5.4)
Czechia	Europe	200542	6 (2.1)	7 (2.5)
Finland	Europe	107224, 107225	5 (1.8)	4 (1.4)

Country	Region	Centers	HZ/su n (%) Total =283	Placebo n (%) Total =279
France	Europe	200621, 200622, 200623, 200625, 200630	11 (3.9)	11 (3.9)
Italy	Europe	107363, 107364, 107365	10 (3.5)	9 (3.2)
Poland	Europe	107545, 107547, 107555	14 (4.9)	16 (5.7)
Spain	Europe	200466, 200467, 200468, 200470, 200471, 200472, 200474, 200475, 201110	30 (10.6)	31 (11.1)
Sweden	Europe	105865, 105866, 106686, 205988	15 (5.3)	11 (3.9)
United Kingdom	Europe	107452, 107453, 107455, 107456, 107458, 200370	24 (8.5)	24 (8.6)
All countries	**Latin America**	**All centers**	**6 (2.1)**	**8 (2.9)**
Panama	Latin America	107105	6 (2.1)	8 (2.9)
All countries	**North America**	**All centers**	**22 (7.8)**	**22 (7.9)**
Canada	North America	107461, 107462, 107726, 200235	9 (3.2)	12 (4.3)
United States	North America	106933, 106940, 106942, 211306	13 (4.6)	10 (3.6)
All countries	**Other**	**All centers**	**47 (16.6)**	**45 (16.1)**
Hong Kong	Other	200314	1 (0.4)	2 (0.7)
Pakistan	Other	200334, 201097	5 (1.8)	5 (1.8)
Russian Federation	Other	200660, 200662, 200666, 200668, 208008, 208009	14 (4.9)	13 (4.7)
Turkey	Other	107169, 107170	27 (9.5)	25 (9.0)

Source: Adapted from BLA 125614/398.0, Zoster-039 CSR, Table 6.3, pp. 1652 – 1655
N = number of subjects with at least one administered dose; n (%) = number/percentage reporting the symptom

Reviewer comment: *Only 23 subjects (4.1%) in the TVC were from the US and 44 subjects (7.8%) were from North America. Regional differences in standard of care may affect vaccine response.*

6.2.7 Surveillance/Monitoring

Study oversight

An Independent Data Monitoring Committee, consisting of clinical experts (independent of the study protocol and external to the Applicant), including two hematology/oncology and one hematology expert, and an independent statistician reviewed semi-blinded safety data (using coded vaccination group names) on an ongoing basis and making recommendations based on the data as to whether to continue, modify or discontinue the trial.

Safety assessment – solicited AEs

Solicited AEs were collected identically to the procedures used in Zoster-002. Please see section 6.1.7 for procedures. Grading of non-ordinal events (pain and general solicited symptoms) and scoring of the maximum intensity of IS redness and swelling were identical to that of Zoster-002. Fever intensity was defined differently than in Zoster-002. Fever was defined as temperature of ≥37.5°C/99.5°F by the oral route. Body temperature for the oral route was graded by the Applicant as follows: Grade 0: <37.5°C, Grade 1: ≥37.5°C - ≤38.0°C, Grade 2: >38.0°C - ≤39.0°C, Grade 3: >39.0°C.

Reviewer comment: *The grading scale for fever for the oral/axillary, or tympanic route is more conservative for higher body temperatures than in Zoster-002 and similar to that found in the*

FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Food and Drug Administration 2007). However, in contrast to FDA guidance, no Grade 4 is defined.

All solicited local (IS) reactions were considered causally related to vaccination.

Safety assessment – unsolicited AEs
The collection and recording of unsolicited AEs, including SAEs and pIMDs, was similar to the procedures used in Zoster-002. Please see section 6.1.7. Differences in the procedures are noted below.

Safety assessment – SAEs
The standard time period for reporting SAEs was from first vaccination to Visit 4/Month 13 (approximately 12 months following administration of last dose of study product).

Safety assessment – AEs of special interest (AESIs) and relapses
Due to the reasons outlined above (section 6.1.7), pIMDs were reported from first vaccination to Visit 4/Month 13 (approximately 12 months following administration of last dose of study product). A list of pIMDs and a pIMD questionnaire were provided to investigators. However, the investigators were to use their medical and scientific judgment to determine whether an AE was a pIMD. On June 30, 2017, the Applicant's list of pIMDs and the customized MedDRA query used to identify events of pIMDs in the clinical database were updated to include Gout and related PTs. Because this list was updated after the study concluded, the prospective reporting of gout and related terms was limited to protocol requirements for AEs (30-days post-vaccination if not serious) or pIMDs (Visit 4/Month 13), if the investigator assessed it as potentially immune-mediated).

Relapses and progression of the hematologic malignancy was defined as a disease-related event and was recorded from Visit 1/M0 until M13/study end.

Pregnancies were reported from M0 until study end at M13 and were followed until conclusion for outcome and any associated SAEs.

Assessment – concomitant medications and vaccinations
The collection of concomitant medications was identical to that in Zoster-002, except that medications collected through study end, beyond M13 in Zoster-002, were collected until study end/M13 in Zoster-039. Any chemotherapy, immunotherapy and/or radiotherapy and associated treatments administered at any time during the study period were also collected in Zoster-039.

Reviewer comment*: The safety monitoring and collection procedures were reviewed and considered acceptable.*

Immunogenicity Assessment
Blood samples were collected at pre-specified timepoints for analyses of the humoral and cellular immune response to vaccination as per the table below.

Table 35. Biological specimens, Zoster-039

Sample Type	Quantity (approximate volume)	Unit	Timepoint	Sub-cohort Name
Blood (Humoral immunology)	8	mL	Visit 1, 2, 3 and 4	All subjects
Blood (Cell-mediated immunology)	30	mL	Visit 1, 2, 3 and 4	CMI sub-cohort
Clinical specimens of HZ lesions	3 replicate samples, taken on the same day, of the highest priority lesion type available: 1) vesicle fluid; 2) crust; 3) crust swab; 4) papule swab	NA	Scheduled in case of suspected HZ for diagnosis	Subjects clinically diagnosed with a suspected HZ case with available lesions

Source: 125614/398.0, Zoster-039 CSR, Table 10, p. 112
NA = Not applicable

HZ incidence Assessment

Please refer to section 6.1.7 for the detailed summary of the methods for collection and adjudication of suspected HZ cases.

6.2.8 Endpoints and Criteria for Study Success

Primary endpoints:

- Occurrence of solicited local and general AEs within 7 days (Days 0-6) after each vaccination in all subjects.
- Occurrence of unsolicited AEs during 30 days (Days 0-29) after each vaccination in all subjects.
- Occurrence of SAEs up to 30 days post-last vaccination in all subjects.
- Occurrence of AEs of specific interest up to 30 days post-last vaccination in all subjects.
- Anti-gE humoral immunogenicity in all vaccinated subjects excluding subjects with NHBCL and CLL.
  - Vaccine response for anti-gE humoral immunogenicity, as determined by ELISA, at Month 2.

    Success criteria: LB of the 95% CI of the VRR for anti-gE ELISA Ab concentrations at Month 2 in the HZ/su vaccine group is at least 60%.

  - Anti-gE Ab concentrations, as determined by ELISA, at Month 2.

    Success criteria: LB of the 95% CI of the geometric mean ratio (GMR) (HZ/su over placebo) for anti-gE ELISA antibody concentrations at Month 2 is greater than 3.

Secondary endpoints:

- Occurrence of SAEs from the first vaccination up to 6 months post-last vaccination in at least 50% of the TVC (the cut-off date of active phase analysis permitted inclusion of safety data from the first vaccination up to 6 months post-second vaccination for 100% of TVC subjects) and from 30 days post-last vaccination until study end in all subjects.
- Occurrence of AEs of specific interest from first vaccination up to 6 months post-last vaccination in at least 50% of the TVC (the cut-off date permitted inclusion of all safety data through this time point in all subjects) and from 30 days post-last vaccination until study end in all subjects.

- Anti-gE Ab concentrations and VRR as determined by ELISA, at Month 2 in all vaccinated subjects excluding subjects with NHBCL.
- Occurrence of confirmed HZ cases from Month 0 until study end.
- Anti-gE Ab concentrations, as determined by ELISA, at Months 0, 1, 2, and 13 and anti-gE Ab VRR as determined by ELISA, at Months 1, 2, and 13 in all vaccinated subjects.
- gE-specific CD4+ T-cell-mediated immunogenicity response in the CMI sub-cohort.
  - Frequencies of gE-specific CD4+ T-cells, expressing at least 2 activation markers (from among IFN-γ, IL-2, TNF-α and CD40L), as determined by in vitro intracellular cytokine staining, at Months 0, 1, 2, and Month 13.
  - Vaccine response for gE-specific CD4+ T-cells expressing at least 2 activation markers (from among IFN-γ, IL-2, TNF-α and CD40L), as determined by in vitro intracellular cytokine staining, at Months 1, 2, and 13.
- Anti-gE Ab concentrations, as determined by ELISA, at Month 0 and at Month 2 in subjects with confirmed HZ. (Anti-gE Ab concentrations were tabulated for all subjects by treatment group for confirmed HZ cases, without matched controls, as a low number of cases was anticipated.)

Reviewer comment: *Some of the secondary endpoints were developed to allow expansion of the study population to accommodate a potential change in primary objective to assess VE based on a disease endpoint. This expansion to a Phase 3 clinical endpoint study was not done.*

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample size assumptions
The assumptions used to determine the sample size for Zoster-039 were based on the post-dose 2 humoral immunogenicity responses from subjects in the HZ/su group in Zoster-001, with adjustments considering the differences in the study populations. The Applicant calculated that 140 evaluable post-dose 2 blood samples would be required from HZ/su group subjects to provide at least 99% power to reach the first humoral VRR objective (excluding subjects with CLL and NHBCL), and 170 evaluable post-dose 2 blood samples would be required from 170 HZ/su group subjects to provide at least 95% power to reach the second humoral VRR objective (excluding subjects with NHBCL).

Missing data
For a given subject and a given efficacy measurement, missing or non-evaluable measurements were not imputed. For the analysis of solicited symptoms, only subjects/doses with documented safety data were included in the analysis. For the analysis of unsolicited AEs and concomitant medications, subjects who did not report an event or medication were considered subjects without an event or medication.

Planned analysis
There were two planned analyses; a first analysis when immunogenicity data up to and including the M2 visit (one month post-dose 2) were available for all subjects and safety data 6 months post-dose 2 were available for 50% of the TVC and an end-of study analysis.

Analysis of efficacy
There was no pre-specified analysis of VE against HZ, however, the incidence of confirmed HZ was an objective, and the incidence rate was determined with reference to the first confirmed HZ case should a subject have more than one episode of HZ. A post-hoc (i.e., unplanned and exploratory) analysis of VE was conducted at the end-of study on subjects in the mTVC. Unlike

the analysis of VE in Zoster-002, subjects were not censored at the time of relapse/disease recurrence for the purposes of the analysis.

Reviewer comment: *Please see the statistical review for their assessment of the acceptability of the statistical methods for the analysis of VE.*

Analysis of immunogenicity
See section 6.1.9 for definitions of serostatus and vaccine response. The VRR was defined as the percentage of subjects who had a vaccine response.

The GMC for anti-gE Ab calculations were performed by taking the anti-log of the mean of the log concentration transformations. The primary population for the analysis of immunogenicity was the ATP cohort for immunogenicity (see section 6.1.9 for a description of the ATP cohort for immunogenicity).

Analysis of safety
Safety analysis was descriptive and was provided overall and by time of occurrence relative to the last vaccination as pre-specified in the study objectives. The primary population for evaluation of safety was the TVC.

Reviewer comment: *Please see the statistical review for further details about the statistical methods used for the immunogenicity and safety analyses. In his review, the statistical reviewer did not comment on the methodology of the analyses of all secondary endpoints; however, the results of these analyses that may be of interest to stakeholders (for example, CMI) are included in this clinical review.*

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

See section 6.1.10.1 for the definitions of the analysis populations. As in Zoster-002, the TVC was the primary population for the analysis of safety and the mTVC was the primary population for the (post hoc) analysis of efficacy. The per protocol population as defined in 6.1.10.1 was the primary analysis population for immunogenicity, however, there were exclusions based on underlying disease for some per-protocol immunogenicity analyses which are specified in sections 6.2.1 and 6.2 8.

Demographics

The summary of demographic characteristics of the TVC is below.

Table 36. Summary of demographic characteristics, Zoster-039 (TVC)

Characteristic	HZ/su N=283 n (%)	Placebo N=279 n (%)	Total N=562 n (%)
Age (years) at dose 1			
Mean (SD)	56.8 (15.5)	57.8 (14.9)	57.3 (15.2)
Median (min, max)	58.0 (19.0, 85.0)	59.0 (18.0, 85.0)	59.0 (18.0, 85.0)
Age stratum			
18 – 49 YOA	74 (26.1)	73 (26.2)	147 (26.2)
≥50 YOA	209 (73.9)	206 (73.8)	415 (73.8)

Characteristic	HZ/su N=283 n (%)	Placebo N=279 n (%)	Total N=562 n (%)
Gender			
Female	114 (40.3)	114 (40.9)	228 (40.6)
Male	169 (59.7)	165 (59.1)	334 (59.4)
Ethnicity			
American Hispanic or Latino	11 (4.0)	15 (5.6)	26 (4.8)
Not American Hispanic or Latino	261 (96.0)	253 (94.4)	514 (95.2)
Missing	11 (-)	11 (-)	22 (-)
Geographic Ancestry			
African Heritage / African American	1 (0.4)	1 (0.4)	2 (0.4)
American Indian or Alaskan Native	0 (0.0)	1 (0.4)	1 (0.2)
Asian - Central / South Asian Heritage	5 (1.8)	6 (2.2)	11 (2.0)
Asian - East Asian Heritage	57 (21.0)	60 (22.4)	117 (21.7)
Asian - South East Asian Heritage	4 (1.5)	1 (0.4)	5 (0.9)
White - Arabic / North African Heritage	0 (0.0)	1 (0.4)	1 (0.2)
White - Caucasian / European Heritage	198 (72.8)	186 (69.4)	384 (71.1)
Other	7 (2.6)	12 (4.5)	19 (3.5)
Missing	11 (-)	11 (-)	22 (-)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 24, p. 174
TVC = total vaccinated cohort; N = total number of subjects; n/% = number / percentage of subjects in a given category; SD = standard deviation

A majority of subjects were male (59.4%), non-Hispanic or Latino (95.2%) and White of Caucasian/European heritage (71.1%).

Reviewer comment: *The median age and proportions of subjects by gender, race and ethnicity were comparable between treatment groups for the TVC. The gender distribution in the study population reflects the greater incidence of hematologic malignancies in men compared to women (National Cancer Institute 2021). Only two subjects of African heritage were enrolled into the study and only 5% of the study population were American Hispanic/Latino. Despite some variability in hematologic malignancy incidence by race and ethnicity (National Cancer Institute 2021), these racial and ethnic subgroups are likely underrepresented in the study population compared to the population of individuals with hematologic malignancies in the US.*

The Applicant provided a summary of demographic characteristics in the mTVC, the population used for the post hoc efficacy analysis. There were no clinically significant differences in demographic characteristics between the TVC and the mTVC or between treatment groups in the mTVC.

The Applicant also provided demographic characteristic summaries by age subgroups,18 – 49 and ≥50 years of age. One hundred and forty-seven subjects (26.2%)18 – 49 YOA were enrolled in the TVC, 74 (26.1%) in the HZ/su group and 73 (26.2%) in the placebo group. Based on the information in the datasets, the number of subjects in the TVC in of the younger age stratum approximately by decade were 38 subjects 18 – 29 YOA (22 in the HZ/su group, 16 in the placebo group), 44 subjects 30 – 39 YOA (22 in the HZ/su group, 22 in the placebo group), and 65 subjects 40 – 49 YOA (30 in the HZ/su group, 35 in the placebo group).

Reviewer comment: *Within each age strata, demographic characteristics were generally similar between treatment groups. Subjects down to age 19 were enrolled into the HZ/su group.*

The Applicant provided demographic characteristics by hematologic malignancy and by timing of vaccination (during or after chemotherapy) in the TVC. No clinically significant between-group differences were noted.

Medical/Behavioral Characterization of the Enrolled Population

The summary of subjects' underlying disease and performance status is presented below.

Table 37. Summary of subjects' underlying disease and performance status, Zoster-039 (TVC)

Characteristics	Parameters or Categories	HZ/su N=283 n (%)	Placebo N=279 n %	Total N=562 n %
Hematological malignancy	Chronic lymphocytic leukaemia (CLL)	42 (14.8)	41 (14.7)	83 (14.8)
	Hodgkin lymphoma	49 (17.3)	47 (16.8)	96 (17.1)
	Multiple myeloma	67 (23.7)	65 (23.3)	132 (23.5)
	Non-Hodgkin B-cell lymphoma	41 (14.5)	39 (14.0)	80 (14.2)
	Non-Hodgkin T cell lymphoma	13 (4.6)	16 (5.7)	29 (5.2)
	Other Hematologic Malignancies	71 (25.1)	71 (25.4)	142 (25.3)
Performance Status ECOG	Fully active*	177 (63.7)	175 (64.3)	352 (64.0)
	Restricted in physically strenuous activity**	94 (33.8)	89 (32.7)	183 (33.3)
	Ambulatory and capable of all selfcare***	6 (2.2)	7 (2.6)	13 (2.4)
	Capable of only limited selfcare****	1 (0.4)	1 (0.4)	2 (0.4)
	Missing	5 (-)	7 (-)	12 (-)
Timing of Vaccination	During the cancer therapy	102 (36.0)	106 (38.0)	208 (37.0)
	After the cancer therapy	181 (64.0)	173 (62.0)	354 (63.0)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 24, p. 174, and Table 6.71, p. 752 – 753
TVC = total vaccinated cohort; N = total number of subjects; n/% = number / percentage of subjects in a given category
ECOG = Eastern Cooperative Oncology Group
* Fully active, able to carry on all pre-disease performance without restriction
** Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work
*** Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
**** Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

Reviewer comment: *Vaccination groups were well-balanced in terms of type of hematologic malignancy and performance status. Subjects with a variety of hematologic malignancies were enrolled, with "other hematologic malignancies" being the highest enrolling category, followed by MM. According to the Leukemia & Lymphoma Society, estimated new cases of hematological malignancies in the U.S. by percentage in 2020 were: lymphoma (48%), leukemia (34%), and MM (18%). Of the estimated new lymphoma cases, 90% were cases of non-Hodgkin's lymphoma and of the estimated new leukemia cases, 37% were CLL, and 32% were AML (American Cancer Society 2020). There are differences between the study population and the US population with new hematologic malignancy diagnoses (for example, Hodgkin lymphoma appears to be over-represented in the study population compared to the proportion of US individuals with new hematologic malignancy diagnoses with Hodgkin Lymphoma and the reviewer was not able to distinguish AML within the 'other' subgroup). But the most common cancers are represented within the study population. Because the number of subjects with a particular malignancy is relatively small, it may be difficult to make conclusions about*

effectiveness and safety of HZ/su for a specific disease. A majority of subjects (64%) were fully active.

The underlying malignancy and performance status in the mTVC were similar to the TVC.

The Applicant presented malignancy and performance status by age and performance status by hematologic malignancy. A majority of subjects 18 – 49 YOA had Hodgkin lymphoma (43.5%) or 'other hematologic malignancies' (29.9%), while a majority of subjects ≥50 YOA had MM (29.9%) or 'other' (23.6%).

Reviewer comment: *There were no clinically significant between-group differences in malignancy or performance status by age or in performance status by malignancy.*

The protocol specified study vaccine was to be administered either during (with at least 10 days between cancer therapy and each vaccination) or after (10 days to 6 months) immunosuppressive chemotherapy, with a minimization procedure employed during randomization. More subjects were vaccinated after receiving immunosuppressive chemotherapy (63.0%) compared to during (37.0%).

Reviewer comment: *There were variations amongst the underlying hematologic malignancy subgroups as to timing of vaccination; however, these variations were consistent between vaccination groups. Subjects with Hodgkin lymphoma and MM made up a greater proportion of the subjects vaccinated after chemotherapy (22.6% and 27.4%, respectively) than during (7.7% and 16.8%, respectively), while subjects with 'other hematologic malignancies' made up a greater proportion of those vaccinated during chemotherapy (36.1%) compared to after (18.9%). Several variables, including timing of vaccination and use of PAT, could affect vaccine effectiveness when analyzed by underlying disease subgroups.*

Subjects were enrolled regardless of whether they were taking prophylactic antiviral therapy (PAT) with activity against HZ. In 125614/398.9, the Applicant provided the distribution of PAT by vaccination group. From the day of dose 1 through study end, any duration of PAT was used by 29.5% of subjects in the mTVC.

Reviewer comment: *Use of PAT is variable across the types of hematologic malignancies and types of therapies represented in this study. Receipt of PAT at any time during the study was similar between the two vaccination groups.*

In the integrated summary of efficacy, the Applicant provided a summary of immunosuppressive treatment subjects in the TVC received (see below).

Table 38. Summary of immunosuppressive treatment received from one year prior to Dose 1 up to the end of the follow-up period, Zoster-039 (mTVC)

Immunosuppressive Treatment	**HZ/su N=259 n (%)**	**Placebo N=256 n (%)**
Allogeneic stem cell transplant	15 (5.8)	14 (5.5)
Anthracyclines	116 (44.8)	102 (39.8)
Anti CD20	77 (29.7)	76 (29.7)
Anti-mitotic agents (including antimicrotubule agents)	93 (35.9)	96 (37.5)
Anti-TNF non-monoclonal antibodies	28 (10.8)	32 (12.5)
Autologous stem cell transplant	16 (6.2)	22 (8.6)
Blinded investigational therapy	2 (0.8)	3 (1.2)

Immunosuppressive Treatment	HZ/su N=259 n (%)	Placebo N=256 n (%)
Calcineurin inhibitors	13 (5.0)	14 (5.5)
Chemotherapy/antineoplastic agents, not specified	2 (0.8)	0 (0)
Folic acid analogues	27 (10.4)	19 (7.4)
Guanine synthesis inhibitors	2 (0.8)	2 (0.8)
Highly immunosuppressive monoclonal Ab	4 (1.5)	3 (1.2)
Nitrogen and mustard analogues	150 (57.9)	148 (57.8)
Nitrosoureas	6 (2.3)	2 (0.8)
Other alkylating agents	52 (20.1)	56 (21.9)
Other cytotoxic antibiotics	43 (16.6)	46 (18.0)
Other selective Immunosuppression (i.e., alemtuzumab)	4 (1.5)	5 (2.0)
Other targeted therapies	22 (8.5)	19 (7.4)
PK inhibitors	3 (1.2)	3 (1.2)
Platinium compound	12 (4.6)	9 (3.5)
Polyclonals	2 (0.8)	2 (0.8)
Proteasome inhibitors	48 (18.5)	45 (17.6)
Purine analogues	51 (19.7)	51 (19.9)
Pyrimidine analogues	65 (25.1)	52 (20.3)
Topoisomerase inhibitors	29 (11.2)	25 (9.8)
Total body irradiation	2 (0.8)	3 (1.2)

Source: Adapted from 125614/398.0, Comprehensive Summary of Efficacy, Table 32, p. 81; and Appendix Table 32, pp. 148 - 150
mTVC = modified total vaccinated cohort; N = total number of subjects; n/% = number / percentage of subjects receiving any immunosuppressive ingredient sub-class at least 1 day within the specified period; TNF = tumor necrosis factor; PK = protein kinase

Reviewer comment: *A variety of therapeutic modalities were used by subjects reflecting the variety of underlying diseases of subjects enrolled. Treatment modalities were generally balanced between treatment groups, although small differences are noted in the proportions of subjects using anthracyclines, pyrimidine analogues, and folic acid analogues. The potential impact of this, if any, on vaccine response is unknown. Approximately 17 – 18% of subjects received a proteasome inhibitor, such as bortezomib, which has an increased risk of HZ, from one year prior to study enrollment through 30 days post-dose 2 and through the end of the study follow-up for efficacy. This is likely reflective of the proportion of the population enrolled with MM. Country and regional variations in treatments for hematologic malignancies may result in differences in HZ risk and immune suppression between the study population and the general US population with hematologic malignancies.*

Subject Disposition

Of the 606 subjects enrolled (total enrolled cohort), 562 were vaccinated and comprised the TVC. Forty-four subjects were enrolled but did not receive vaccine.

Of the 562 subjects included in the TVC, a total of 452 subjects (80.4%) completed the study and 110 (19.6%) were withdrawn. The number of subjects withdrawn and reasons for withdrawal by treatment group are presented below.

Table 39. Number of subjects vaccinated, completed up to the study end, and withdrawn with reason for withdrawal, Zoster-039 (TVC)

	HZ/su n (%)	Placebo n (%)	Total n (%)
Number of subjects vaccinated	283 (100)	279 (100)	562 (100)
Number of subjects completed	236 (83.4)	216 (77.4)	452 (80.4)
Number of subjects withdrawn	47 (16.6)	63 (22.6)	110 (19.6)
Reasons for withdrawal			
Serious Adverse Event	26 (9.2)	35 (12.5)	61 (10.9)
Non-Serious Adverse Event	3 (1.1)	4 (1.4)	7 (1.2)
Protocol violation	2 (0.7)	0 (0.0)	2 (0.4)
Consent withdrawal (not due to an adverse event)	9 (3.2)	14 (5.0)	23 (4.1)
Migrated/moved from study area	0 (0.0)	3 (1.1)	3 (0.5)
Lost to follow-up (subjects with incomplete vaccination course)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up (subjects with complete vaccination course)	6 (2.1)	4 (1.4)	10 (1.8)
Suspected HZ episode*	0 (0.0)	1 (0.4)	1 (0.2)
Others	1 (0.4)	2 (0.7)	3 0.5)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 23, p. 164
TVC = total vaccinated cohort; N = number of subjects in each group or in total; n/% = number / percentage of subjects with the specified disposition or reason for withdrawal
* One subject withdrawn due to a serious suspected HZ episode

Reviewer comment: *The high withdrawal rate (19.6%) may be reflective of the study population, including subjects recently diagnosed with malignancy and subjects currently receiving chemotherapy. SAE was the most common reason for withdrawal (11%), followed by consent withdrawal (4%). None of the non-serious AEs or SAEs leading to withdrawal were assessed as related to vaccination by investigators. The placebo group had a slightly higher rate of withdrawal by the study end compared to the HZ/su group, though the reasons subjects were withdrawn were distributed similarly between vaccine groups. This slightly higher withdrawal rate in the placebo group was seen in each age stratum (18 – 49 and ≥50 YOA), in subjects who were vaccinated during and after receiving chemotherapy, and in subjects with an underlying disease of 'MM and other diagnoses,' the largest subgroup. Few subjects were withdrawn from the CLL and NHBCL groups.*

Exposure

A total of 46 (8.2%) subjects out of 562 in the TVC did not receive the second vaccination; 24 (8.5%) in the HZ/su group and 22 (7.9%) in the placebo group.

Table 40. Number and percentage of subjects who received one or both study vaccine doses, Zoster-039 (TVC)

Total Doses Received	HZ/su N=283 n (%)	Placebo N=279 n (%)	Total N=562 n (%)
1	24 (8.5)	22 (7.9)	46 (8.2)
2	259 (91.5)	257 (92.1)	516 (91.8)
Any	283 (100)	279 (100)	562 (100)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 10.1, p. 904
TVC = total vaccinated cohort; N = number of subjects in each group or in total; n/% = number/percentage of subjects receiving the specified total number of doses

Reviewer comment: *Most subjects in each treatment group received both doses. Exposure by age stratum (18 – 49 YOA and ≥50 YOA) was reviewed. Similar proportions of subjects in each treatment group and in each age stratum received both doses (91.4 – 92.2%).*

The reasons subjects in the TVC did not receive a second vaccination are displayed below by vaccination group.

Table 41. Number and percentage of subjects who were withdrawn from vaccination (did not receive dose 2) with reason for withdrawal, Zoster-039 (TVC)

	HZ/su N=283 n (%)	Placebo N=279 n (%)
Did not receive dose 2	24 (8.5)	22 (7.9)
Reason dose 2 not administered		
SAE or pIMD	0	0
Non-serious adverse event	1 (0.4)	4 (1.4)
Non-serious suspected HZ Episode	3 (1.1)	3 (1.1)
Other	7 (2.5)	3 (1.1)
Visit not done	13 (4.6)	12 (54.5)
Visit not done reason		
SAE or pIMD	5 (1.8)	3 (1.1)
Non-serious AE	2 (0.7)	2 (0.7)
Consent withdrawn	5 (1.8)	6 (2.2)
Protocol violation	1 (0.4)	0
Suspected HZ Episode	0	1 (0.4)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 6.81, pp. 769 - 770
TVC = total vaccinated cohort; N = number of subjects in each group or in total; n/% = number/percentage of subjects withdrawn from vaccination for the specified reason

Reviewer comment: *As in Zoster-002, the Applicant presented reasons for vaccine withdrawal separate from reasons no vaccination visit was completed. Four SAEs in the HZ/su group and two in the placebo group that led to no M1 visit were fatal events. In the HZ/su group, one subject developed thrombocytopenia and acute relapse of AML six days after dose 1, both fatal events. One subject died of sepsis which started 44 days after dose 1 (see section 6.2.12.3). Two other subjects had a relapse or progression which eventually was fatal. A 57 YOA man did not return for the M1 visit due to a non-serious AE of presyncope on the day of dose 1, which was assessed by the investigator as unrelated to vaccination. None of the SAEs or non-serious AEs that led to subjects not receiving dose 2 visit were assessed by investigators as related. Overall, the proportions of subjects not receiving dose 2 and reasons are similar between groups, with the exception of more SAEs leading to visit not done (see above) and 'other' reason for discontinuation. Other reasons in the HZ/su group included: protocol violation (n=2), "uncertainty" regarding a suspected episode of HZ that was not confirmed, planned autoHCT, consent withdraw, and unable to allocate vial. One subject who withdrew from vaccination for an unclear 'other' reason ("Per Protocol, patient was under immunosuppression") reported an unsolicited AE of elevated CRP assessed as related. The reviewer did not identify safety concerns in the reasons for withdrawal from vaccination.*

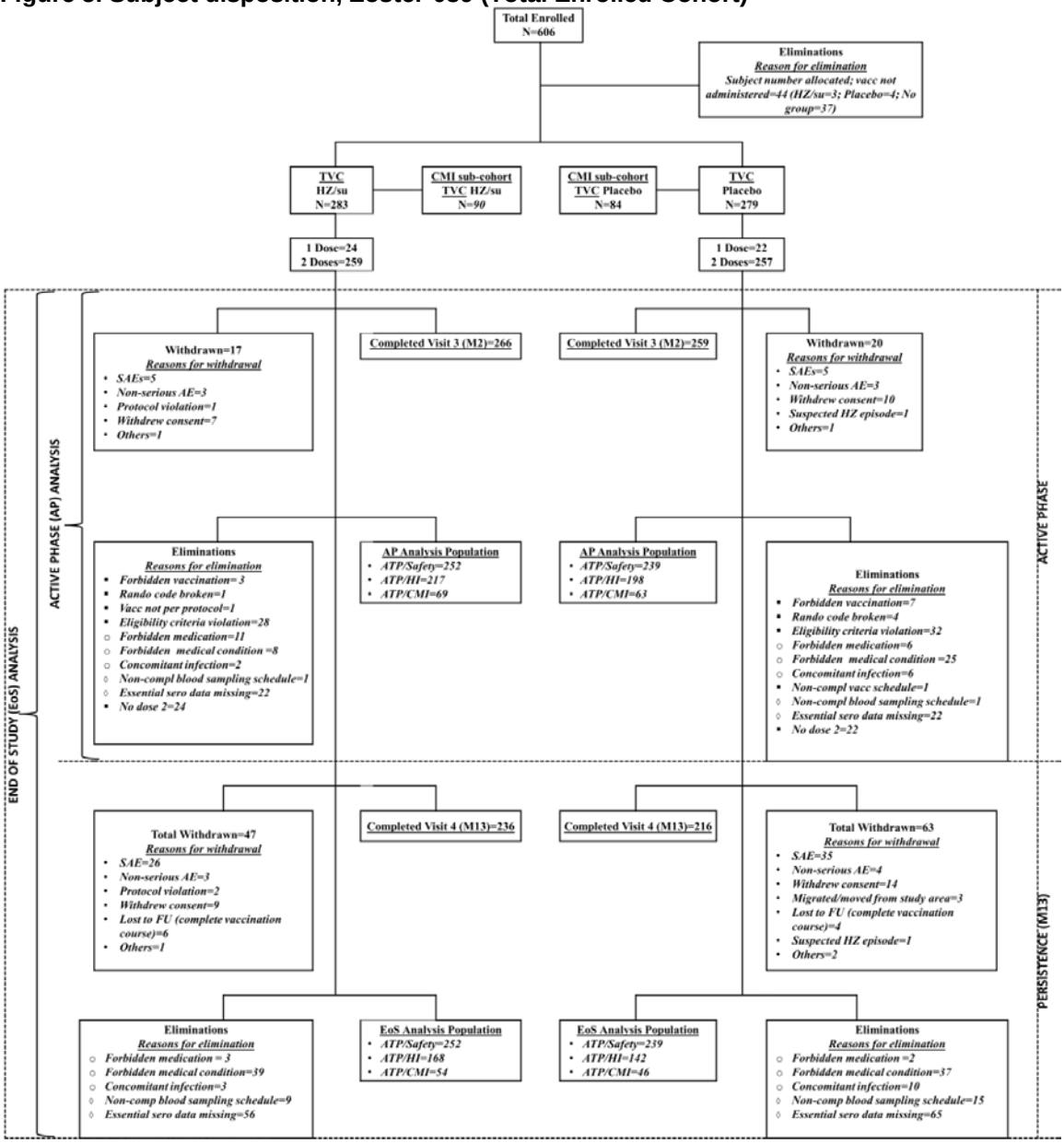
<u>mTVC population (post hoc analysis)</u>
Overall, 515 subjects (91.6% of the TVC), 259 subjects (91.5%) and 256 subjects (91.8%) of subjects in the TVC of the HZ/su and placebo groups, respectively, were included in the mTVC for the analysis of efficacy. One subject from the placebo group ((b) (6)) was excluded because he reported a confirmed HZ case prior to 30 days following dose 2. The remainder of subjects were excluded due to not receiving two doses.

Reviewer comment: *The proportion of subjects in the TVC that were included in the mTVC for the analysis of efficacy was comparable between treatment groups.*

Protocol deviations

The figure below shows the number of subjects included in the total enrolled cohort, the TVC, the ATP cohort for safety, the ATP cohort for humoral immunogenicity, and the ATP cohort for cellular immunity with reasons for exclusion.

Figure 5. Subject disposition, Zoster-039 (Total Enrolled Cohort)



Source: 125614/398.0, Zoster-039 CSR, Figure 3, page 171
N = number of subjects; TVC = total vaccinated cohort; CMI = cell mediated immunogenicity; M = month; SAE = serious adverse event; AE = adverse event; AP = active phase; ATP = according to protocol cohort; HI: humoral immunogenicity; Rando = randomization; Vacc = vaccination; Med cond = medical condition; Non-comp = non-compliant; Sero = serology; FU = follow-up

Elimination: Subjects were permanently eliminated from the ATP cohort for safety and ATP cohort for immunogenicity/persistence due to eligibility criteria violation, receiving other vaccine forbidden in the protocol, randomization code broken and if vaccine dose was not administered per protocol. In addition, subjects were permanently eliminated from the ATP cohort for humoral immunogenicity/persistence due to concomitant infection related to the vaccine which may influence immune response, concomitant medication, forbidden underlying condition and no dose 2. Subjects were eliminated from the ATP cohort for immunogenicity at the given timepoint (not permanently and may have been included at the other timepoints) due to non-compliance with blood sampling schedule and essential serology data missing.
Withdrawn: Subjects could be withdrawn from treatment for SAEs/non-serious AEs, protocol violation, consent withdrawal (not due to an AE), migration from study area, lost to follow-up, suspected HZ episode and fatal SAEs.
A progressive counting was used for the eliminations from the ATP cohort. Different bullet points are used to differentiate the type of elimination code: ■ for permanent codes, which are counted at the active phase and are permanent across phases (so not listed at persistence phase in the diagram); ○ for progressive codes, where the persistence phase values were obtained by subtracting the corresponding active phase values from the ATP cohort for humoral persistence and ◊ for specific-to-phase codes, which have specific value at each phase.

Reviewer comment: *Reasons for exclusion from the ATP cohorts for humoral immunogenicity were generally similar between groups, with the exception of "forbidden medical condition" (one that could confound the immune response to study vaccine, or its interpretation, such as HZ or an unplanned HCT) being more common in subjects in the placebo group.*

Protocol deviations not leading to elimination from analyses (section 6.3.2 of the CSR) were also reviewed. These deviations involved informed consent forms, late reporting of safety events, eligibility criteria, diary card completion, and biologic specimen collection and processing.

Reviewer comment: *The Applicant's documentation of the deviations not leading to exclusion from analyses as well as corrective actions taken were reviewed and found to be acceptable.*

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The co-primary immunogenicity objectives, VRR and GMC ratio of anti-gE humoral immune responses at Month 2, were assessed on the ATP cohort for humoral immunogenicity, excluding subjects with NHBCL and CLL.

Table 42. Vaccine response rates for anti-gE antibody ELISA concentrations at Month 2 in subjects with hematologic malignancies excluding subjects with Non-Hodgkin B-cell Lymphoma and Chronic Lymphocytic Leukemia, Zoster-039 (ATP cohort for humoral immunogenicity)

Test Description	Group	N	VRR n	VRR %	VRR LB 95% CI	VRR UB 95% CI
VZV.gE Ab.IgG	HZ/su	148	119	80.4	73.1	86.5
VZV.gE Ab.IgG	Placebo	130	1	0.8	0.0	4.2

Source: 125614/398.0, Zoster-039 CSR, Table 26, p. 182
ATP = according to protocol; N = number of subjects with pre- and post-vaccination results available; VRR = vaccine response rate; n/% = number/percentage of subjects with a vaccine response; 95% CI = exact 95% confidence interval; LB = Lower Bound; UB = Upper Bound
Vaccine response defined as:
For initially seronegative subjects, antibody concentrations at Month 2≥4 fold the cut-off for anti-gE (4x97 mIU/mL)
For initially seropositive subjects, antibody concentrations at Month 2≥4 fold the pre-vaccination antibody concentration

The first co-primary immunogenicity objective was met since the success criterion, LB of the 95% CI of the humoral VRR for anti-gE Ab ELISA concentrations in the HZ/su group at Month 2 was ≥60%.

Table 43. Adjusted geometric means and ratio of HZ/su over placebo for anti-gE antibody ELISA concentrations at Month 2 in subjects with hematologic malignancies excluding subjects with Non-Hodgkin B cell lymphoma and chronic lymphocytic leukemia, Zoster-039 (ATP cohort for humoral immunogenicity)

Timing	Group	N	AGM Value	AGM LB 95% CI	AGM UB 95% CI	AGMR Value	AGMR LB 95% CI	AGMR UB 95% CI
PII(M2)	HZ/su	148	23132.9	16642.8	32153.9	29.75	21.09	41.96
PII(M2)	Placebo	130	777.6	702.8	860.3	-	-	-

Source: 125614/398.0 Zoster-039, CSR Table 27, p. 182
ATP = according to protocol; N = number of subjects within a group with results available; AGM = adjusted geometric mean; AGMR = adjusted geometric mean ratio; 95% CI = exact 95% confidence interval; LB = Lower Bound; UB = Upper Bound

The second co-primary immunogenicity objective was met since the success criterion, LB of the 95% CI of the GM ratio (HZ/su over placebo) for anti-gE Ab ELISA concentrations in the HZ/su group at Month 2 was greater than 3.

6.2.11.2 Analyses of Secondary Endpoints

Cell-mediated Immunogenicity (CMI)
CMI was assessed in a subset of subjects, those in the Adapted ATP cohort for immunogenicity – CMI. The median (minimum – maximum) fold increase over pre-vaccination in the frequency of gE-specific CD4 T-cells was 6.9 (0.0 – 2,795.2), 45.9 (0.0 – 11,808.3), and 21.4 (0.0 – 5,558.4) at Months 1, 2, and 13 based on 33 – 48 subjects at each time point. In the placebo group, the observed median (minimum – maximum) fold increase over pre-vaccination was not higher than 1.0 (0 – 6,989.6) at any timepoint based on 31 – 47 subjects at each time point. In the HZ/su group, the VRR (defined as at least a two-fold increase in T cell frequencies compared to the threshold or pre-vaccination frequencies for subjects with pre-vaccination frequencies below or above threshold, respectively) in the frequency of gE-specific CD4 T-cells was 37.5% (95% CI: 24.0%, 52.6%), 83.7% (95% CI: 69.3, 93.2%), and 66.7% (95% CI: 48.2, 82.0%) at Months 1, 2, and 13. In the placebo group, the VRR point estimate was not higher than 6.8% at any timepoint.

Cell-mediated Immunogenicity (CMI) by underlying disease: At M2, in the HZ/su group, the median fold increase over pre-vaccination in the frequency of gE-specific CD4 T-cells by underlying disease subgroups was 31.0 based on 17 subjects with NHBCL, 53.9 based on 19 subjects with 'MM and other diseases," and 93.7 based on 7 subjects with CLL. In the placebo group, the median (minimum – maximum) fold increase over pre-vaccination was not higher than 1.1 (0 – 6,989.6) in each subgroup. At M2, in the HZ/su group, the VRR (see definition above) in the frequency of gE-specific CD4 T-cells by underlying disease subgroups was 71.4% (95% CI: 29.0%, 96.3%) based on 7 subjects with CLL, 73.7% (95% CI: 48.8%, 90.9%) based on 19 subjects with 'MM or other diseases,' to 100% (95% CI: 80.5%, 100%) based on 17 subjects with NHBCL. In the placebo group, at M2 the VRR point estimate was not higher than 12.5% in each subgroup.

Reviewer comment: *In the CMI subset, immune responses were demonstrated following HZ/su in each of the three underlying disease subgroups.*

CMI by age strata and timing of cancer therapy: For subjects in the two age strata, after HZ/su administration, gE-specific CMI responses relative to the pre-vaccination, were observed at 1 month following the first dose, increased following the second dose and remained above pre-vaccination levels through one year post-dose 2. There was a trend toward increased gE-

specific CMI response following vaccination with HZ/su in the 18 – 49 YOA group compared to the ≥50 YOA group.

For subjects in the two strata of timing of vaccination relative to cancer therapy, after HZ/su administration, gE-specific CMI responses relative to the pre-vaccination, were observed at 1 month following the first dose, increased following the second dose and remained above pre-vaccination levels through one year post-dose 2. There was a trend toward increased gE-specific CMI response following vaccination with HZ/su in subjects receiving HZ/su after cancer therapy compared to subjects receiving HZ/su during cancer therapy.

6.2.11.3 Subpopulation Analyses

Immunogenicity by disease
The table below shows the GMC and VRR by vaccination group and underlying disease.

Table 44. Geometric mean concentrations and vaccine response rates for anti-gE antibody at Month 0, 1, 2 and 13 by underlying diseases stratum, Zoster-039 (adapted ATP cohort for Humoral immunogenicity)

Sub-group	Group	Timing	GMC N	GMC value	GMC LB 95% CI	GMC UB 95% CI	VRR N	VRR n	VRR %	VRR LB 95% CI	VRR UB 95% CI
MM and other diseases	HZ/su	PRE	148	913.8	736.9	1133.2					
		PI(M1)	147	6786.3	5080.7	9064.6	147	88	59.9	51.5	67.9
		PII(M2)	148	24450.7	17991.9	33228.1	148	119	80.4	73.1	86.5
		PII(M13)	113	7127.9	5361.2	9476.7	111	74	66.7	57.1	75.3
	Placebo	PRE	130	810.5	653.0	1006.1	-	-	-	-	-
		PI(M1)	129	743.3	599.6	921.5	129	0	0.0	0.0	2.8
		PII(M2)	130	737.0	587.3	924.8	130	1	0.8	0.0	4.2
		PII(M13)	92	858.7	656.2	1123.7	90	5	5.6	1.8	12.5
CLL	HZ/su	PRE	36	928.6	614.0	1404.3	-	-	-	-	-
		PI(M1)	36	1134.7	734.6	1752.9	36	2	5.6	0.7	18.7
		PII(M2)	36	2620.7	1287.9	5332.9	36	8	22.2	10.1	39.2
		PII(M13)	25	2234.2	1210.5	4123.6	25	5	20.0	6.8	40.7
	Placebo	PRE	35	1008.6	663.3	1533.7	-	-	-	-	-
		PI(M1)	35	1013.5	669.7	1533.8	35	0	0.0	0.0	10.0
		PII(M2)	35	1032.2	680.6	1565.5	35	0	0.0	0.0	10.0
		PII(M13)	25	1119.8	707.9	1771.4	25	0	0.0	0.0	13.7
NHBCL	HZ/su	PRE	33	1275.8	908.5	1791.5	-	-	-	-	-
		PI(M1)	32	2074.3	1433.4	3001.7	32	5	15.6	5.3	32.8
		PII(M2)	33	5476.9	2985.7	10046.8	33	15	45.5	28.1	63.6
		PII(M13)	29	3161.7	1703.9	5866.7	29	7	24.1	10.3	43.5
	Placebo	PRE	33	1079.3	835.2	1394.8	-	-	-	-	-
		PI(M1)	32	996.9	764.7	1299.6	32	0	0.0	0.0	10.9
		PII(M2)	33	1067.3	820.7	1387.9	33	0	0.0	0.0	10.6
		PII(M13)	25	835.2	593.8	1174.8	25	0	0.0	0.0	13.7

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 7.11, p. 787; and Table 7.12, p. 788
GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects within a group with results available; MM = Multiple myeloma; CLL = Chronic Lymphocytic Leukemia; NHBCL = Non-Hodgkin B-cell Lymphoma; 95% CI = exact 95% confidence interval; LB = Lower Bound; UB = Upper Bound; n/% = Number / percentage of subjects with a vaccine response; PRE = pre-vaccination (Month 0); PI(M1) = post-vaccination Dose I (Month 1); PII(M2) = post-vaccination Dose II (Month 2); PII(M13) = post-vaccination Dose II (Month 13)
Vaccine response defined as:
For initially seronegative subjects, antibody concentrations at post-vaccination ≥4 fold the cut-off for Anti-gE (4x97 mIU/mL)
For initially seropositive subjects, antibody concentrations at post-vaccination ≥4 fold the pre-vaccination antibody concentration

Reviewer comment: *Subjects with CLL and NHBCL had a poor anti-gE Ab response to HZ/su vaccination compared to subjects with MM and other diseases.*

Humoral immunogenicity by age and timing: For subjects in the two age strata, after HZ/su administration, anti-gE humoral immune responses were observed 1 month following the first dose, with further increase after the second dose and persisted through one year post-dose 2, relative to pre-vaccination levels. Within the HZ/su group, there was a trend towards a higher anti-gE humoral immune response in the 18 – 49 YOA age strata than the ≥50 YOA age strata.

For subjects in the two strata for timing of vaccination in relation to the cancer therapy cycle, after HZ/su administration, anti-gE humoral immune responses were observed 1 month following the first dose; with further increase after the second dose and persisted through one year post-dose 2, above pre-vaccination levels. Within the HZ/su group, there was a trend towards a higher anti-gE humoral immune response in subjects vaccinated after completion of immunosuppressive therapy than in subjects vaccinated during cancer therapy course.

6.2.11.4 Dropouts and/or Discontinuations

With respect to the co-primary endpoints for humoral immunogenicity assessed at M2, 94.0% of the HZ/su group and 92.8% of the placebo group completed this visit. The ATP cohort for humoral immunogenicity included 76.7% of HZ/su recipients and 71.0% of placebo recipients. As more than 5% of subjects were excluded from this cohort, an analysis of humoral immunogenicity was performed on the TVC and was consistent with the analysis based on the ATP cohort.

With respect to HZ incidence and the post hoc analysis of VE for the prevention of HZ which was assessed for the study duration (see section 6.2.11.5), only 83.4% of HZ/su recipients and 77.4% of placebo recipients completed the study. However, 91.5% of HZ/su recipients and 91.8% of placebo recipients were included in the mTVC for the analysis of efficacy. Subjects were censored from the analysis at the time of their last visit if they dropped out.

Reviewer comment: *The high study withdrawal rate is not unexpected in this population of subjects recently diagnosed with cancer and undergoing or recently completed chemotherapy. The Applicant accounted for the study withdrawals in the post hoc analysis.*

6.2.11.5 Exploratory and Post Hoc Analyses

HZ incidence
HZ incidence was collected as a pre-specified secondary objective but is presented here with the post hoc analysis of efficacy because of the clinical relevance to that analysis.

From Month 0, 9 of 283 subjects in the HZ/su and 25 of 279 subjects in the placebo groups had a suspected episode of HZ. Of these, 6 subjects in the HZ/su and 19 subjects in the placebo groups had a confirmed episode of HZ. A majority of cases in each group were confirmed by PCR. Incidence rates in the TVC, were calculated to be 20.24 HZ cases per 1000 PY (95% CI: 9.09, 45.06) in the HZ group and 70.9 HZ cases per 1000 PY (95% CI: 45.20, 111.11) in the placebo group.

Reviewer comment: *The incidence of HZ in both groups was calculated to be higher than rates reported in this population in the literature (12.0 per 1000 PY [95% CI:11.5, 12.5], Muñoz-Quiles 2020). This incidence includes HZ episodes occurring prior to 30 days post-dose 2.*

HZ complications and suspected HZ without the characteristic rash, including SAEs associated with these events, were captured as adverse events. Of the suspected cases of HZ, no cases were serious in the HZ/su group and three cases, including one case which was not confirmed as HZ, were serious in the placebo group. Of the six subjects with confirmed HZ cases in the HZ/su group, three reported HZ-related complications, including one in a subject who had received two vaccinations. A 67 YO man with CLL who completed chemotherapy prior to first vaccination, reported HZ and PHN starting 281 days after the second dose of HZ/su. The other two HZ/su recipients who reported HZ complications only received one dose of HZ/su (one subject with PHN and one subject with disseminated HZ and PHN). Of the 19 confirmed cases in the placebo group, 4 subjects reported PHN, 2 at least 30 days after receiving dose 2. Therefore, after both doses, 1 of 2 confirmed HZ cases in the HZ/su group and 2 of 14 HZ cases in the placebo group reported PHN and none reported other complications.

Reviewer comment: *A lower proportion of subjects with confirmed HZ reported HZ complications, including PHN, in the placebo group compared to the HZ/su group. The sample size of subjects with confirmed HZ is too small to draw conclusions about this difference.*

Post hoc analysis of vaccine efficacy

From 30 days following dose 2, in the mTVC, 2 subjects in the HZ/su and 14 subjects in the placebo groups had confirmed HZ cases after a median (minimum – maximum) follow-up time of 11.1 (0-15.6) months. The table below shows the VE in prevention of HZ.

Table 45. Vaccine efficacy for prevention of first or only episode of HZ from 30 days after the second vaccination until study end using Poisson method, Zoster-039 (mTVC)

HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LB 95% CI	VE UB 95% CI
259	2	236.1	8.5	256	14	211.6	66.2	87.2	44.2	98.6

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 8.9, p. 897mTVC = modified total vaccinated cohort; N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years; n/T (per 1000) = incidence rate of subjects reporting at least one event; 95% CI = 95% confidence interval; LB = Lower Bound; UB = Upper Bound; VE (%) = Vaccine Efficacy (Poisson method)

Reviewer comment: *Vaccine efficacy against HZ was demonstrated in this population of subjects with hematologic malignancies who were taking or recently had completed immunosuppressive cancer therapy.*

The Applicant did not provide analyses of VE in prevention of HZ by subgroups in the CSR, but did provide the HZ incidence by subgroups, which includes subjects with confirmed HZ reported prior to 30 days post-dose 2. By age strata (18 – 49 and ≥50 YOA), underlying disease (CLL, NHBCL, and MM and other diseases), and timing of vaccination with respect to cancer therapy (during and after), in each subgroup, the HZ incidence point estimate was higher in the placebo group than the HZ/su group, although CIs overlapped. For subjects 18 – 49 YOA, 3 confirmed cases of HZ resulted in an incidence of 37.3 per 1,000 PY (95% CI: 12.0, 115.7) in the HZ/su group and 4 confirmed cases of HZ resulted in an HZ incidence of 54.8 per 1000 PY (95% CI: 20.6, 146.0) in the placebo group. The confirmed HZ case distribution 30 days post-dose 2 in this age strata was 1 case in the HZ/su group and 2 cases in the placebo group. In other strata, HZ incidences by vaccination group were similar to the incidence in the study population.

Reviewer comment: *The incidence in the 18 – 49 YOA HZ/su group is higher than the ≥50 YOA HZ/su group, suggesting that this finding may be due to the small number of cases. The*

incidence of HZ in this study was too low to draw conclusions about VE based on subgroups, particularly for the 18 – 49 YOA subgroup.

6.2.12 Safety Analyses

6.2.12.1 Methods

6.2.12.2 Overview of Adverse Events

The TVC, the primary population for the assessment of safety, included 562 subjects total, 283 in the HZ/su group and 279 in the placebo group.

Solicited Adverse Events
Compliance with return of local symptom sheets and general symptom sheets for reactogenicity assessments for both treatment groups was above 95% (range 96.1% to 98.5%) following each dose and overall. Compliance with symptom sheet return by age strata was reviewed and was 95.3% or greater for each age stratum, symptom screener (local or general), dose, and treatment group.

Overall solicited AEs: Overall by subject, both doses considered, 90.3% and 51.8% of subjects in the HZ/su and placebo groups, respectively, reported at least one solicited symptom of any grade during the seven-day post-vaccination period. At least one local symptom was reported by 83.8% and 17.5% of subjects in the HZ/su and placebo groups, respectively, and at least one general solicited symptom was reported by 74.1% and 48.9% of subjects in the HZ/su and placebo groups, respectively. The percentage of subjects in the HZ/su group reporting any solicited symptom, any solicited local symptom, and any solicited general symptom after dose 1 as compared to dose 2 was 81.3% vs. 82.8%, 75.5% vs. 71.8%, and 58.3% vs. 67.1%, respectively.

Reviewer comment: *In this study population of subjects with hematologic malignancies, approximately half of subjects in the placebo group reported general symptoms. Both local and general symptoms were reported at greater rates in the HZ/su group. Proportions of subjects in the HZ/su group reporting solicited general symptoms was higher following dose 2 compared to dose 1. This increase in solicited general symptoms following dose 2 compared to dose 1 was not observed in the placebo group. The proportions of subjects reporting any grade local solicited symptoms in the HZ/su group was comparable following dose 1 as compared to dose 2.*

The proportions of HZ/su recipients reporting any solicited symptom during the 7-day post-vaccination period by age strata overall by subject, both doses considered, was 94.6% and 88.7% for the age strata 18 – 49 YOA and ≥50 YOA, respectively. The percentage of HZ/su recipients reporting any local solicited symptoms during the 7-day post-vaccination period was 93.2% and 80.4% for the age strata 18 – 49 YOA and ≥50 YOA, respectively. The percentage of HZ/su recipients reporting any general solicited symptom during the 7-day post-vaccination period was 81.1% and 71.6% for the age strata 18 – 49 YOA and ≥50 YOA, respectively. There was a trend toward more subjects in the HZ/su group in both age strata reporting any general solicited symptom following dose 2 compared to dose 1 (66.2% vs. 73.5% in subjects 18 – 49 YOA and 55.4% vs. 64.7% in subjects ≥50 YOA following dose 1 and dose 2, respectively).

Reviewer comment: *In this population of subjects with hematologic malignancies, the proportions of subjects reporting any, any local, or any general symptom in the HZ/su group was*

higher in the younger compared to the older age strata. In both age strata, solicited general symptoms tended to be reported more frequently following dose 2.

Overall by subject, both doses considered, 21.9% and 6.2% of subjects in the HZ/su and placebo groups reported a Grade 3 solicited symptom. At least one Grade 3 solicited local symptom was reported by 13.3% and 0% of subjects in the HZ/su and placebo groups, respectively, and at least one Grade 3 solicited general symptom was reported by 15.5% and 6.2% of subjects in the HZ/su and placebo groups, respectively. The percentage of subjects in the HZ/su group reporting any Grade 3 solicited symptom, any Grade 3 solicited local symptom, and any Grade 3 solicited general symptom after dose 1 as compared to dose 2 was 10.8% vs. 18.4%, 6.5% vs. 10.6%, and 7.2% vs. 13.3% respectively.

Overall by subject and by age in the HZ/su group, both doses considered, 23.0% and 21.6% of HZ/su recipients 18 – 49 YOA and ≥50 YOA, respectively, reported at least one Grade 3 solicited symptom. At least one Grade 3 solicited local symptom was reported by 13.5%, and 13.2% of HZ/su recipients 18 – 49 YOA and ≥50 YOA respectively, while at least one Grade 3 solicited general symptom was reported by 16.2%, and 15.1% of HZ/su recipients 18 – 49 YOA and ≥50 YOA, respectively. For the 18 – 49 YOA stratum, the proportion of subjects reporting any Grade 3 solicited symptoms and any Grade 3 solicited general symptoms increased following dose 2 compared to dose 1; Grade 3 solicited local symptoms did not increase with dose number in this age stratum. For ≥50 YOA stratum, any Grade 3 solicited symptoms, any Grade 3 local symptoms, and any Grade 3 solicited general symptoms increased following dose 2 comparted to dose 1.

Reviewer comment: *Overall by subject in this population, Grade 3 reactogenicity was common in both age strata following HZ/su administration. In the younger age stratum, the post-dose 2 increase in solicited symptoms was driven by an increase in Grade 3 general solicited symptoms only, whereas in the older age stratum, both Grade 3 local and general solicited symptoms increased following dose 2 compared to dose 1.*

The Applicant performed an analysis of the proportions of subjects reporting solicited symptoms lasting beyond the seven-day post-vaccination period. Overall per subject, both doses considered, 19.1%, 7.1% and 13.4% of HZ/su recipients reported at least one solicited symptom, solicited local symptom, and solicited general symptom, respectively, beginning in and lasting beyond the 7-day solicited reporting period. Overall per subject, 5.3%, 1.4% and 3.9% of HZ/su recipients reported at least one Grade 3 solicited symptom, Grade 3 solicited local, and Grade 3 solicited general symptom, respectively, beginning in and lasting beyond this period.

Reviewer comment: *The proportion of subjects in the HZ/su group reporting general solicited symptoms (13.4%) and Grade 3 general solicited symptoms (3.9%) lasting beyond the seven-day assessment period is similar to that reported in the placebo group (12.9% and 3.6%, respectively) and so may be attributable to the study population. The proportion of subjects in the HZ/su group reporting solicited symptoms lasting beyond the seven-day assessment period was similar following dose 2 compared to dose 1 (data not shown).*

Solicited local symptoms: Overall by subject, both doses considered, at least one solicited local symptom was reported by 83.8% and 17.5% of subjects in the HZ/su group and placebo group, respectively, and at least one Grade 3 solicited local symptom was reported by 13.3% and 0% of subjects in the HZ/su and placebo groups, respectively. The numbers and proportions of

subjects in the TVC reporting any grade and Grade 3 individual solicited local symptoms are below.

Table 46. Incidence of solicited local symptoms reported during the 7-day post-vaccination period overall by subject, both doses considered, Zoster-039 (TVC)

Solicited Symptom	Grade	HZ/su N	HZ/su n	HZ/su %	Placebo N	Placebo n	Placebo %
Pain	Any	278	221	79.5	274	45	16.4
	Grade 3	278	29	10.4	274	0	0
Redness (mm)	Any grade	278	115	41.4	274	5	1.8
	>100	278	12	4.3	274	0	0
Swelling (mm)	Any grade	278	63	22.7	274	2	0.7
	>100	278	5	1.8	274	0	0

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 35, pp. 209 – 210
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n/% = number / percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
Any grade redness and swelling includes subjects with events measured ≥20 mm, or reported as present with missing measurements.

Overall by subject, pain was the most commonly reported local solicited symptom reported by subjects in both the HZ/su and placebo groups (79.5% and 16.4% of subjects, respectively). The table below shows the number and proportion of subjects in the HZ/su group reporting any grade and Grade 3 individual solicited local symptoms following dose 1 and 2.

Table 47. Incidence of solicited local symptoms reported in the HZ/su group during the 7-day post-vaccination period following dose 1 and dose 2 overall by subject, Zoster-039 (TVC)

Solicited Symptom	Grade	Dose 1 N	Dose 1 n	Dose 1 %	Dose 2 N	Dose2 n	Dose2 %
Pain	All	278	199	71.6	255	172	67.5
	Grade 3	278	16	5.8	255	20	7.8
Redness (mm)	Any grade	278	80	28.8	255	82	32.2
	>100	278	2	0.7	255	10	3.9
Swelling (mm)	Any grade	278	47	16.9	255	42	16.5
	>100	278	1	0.4	255	5	2.0

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 35, pp. 209 – 210
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n/% = number / percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
Any grade redness and swelling includes subjects with events measured ≥20 mm, or reported as present with missing measurements

Reviewer comment: *As stated above, the proportion of subjects in the HZ/su group reporting any local solicited symptom did not increase following dose 2 compared to dose 1. Similarly, the proportion of subjects reporting any pain and Grade 3 pain was generally similar following dose 2 compared to dose 1. However, the proportion of subjects reporting any and Grade 3 redness or swelling did increase slightly after dose 2 compared to dose 1. The proportion of subjects reporting grade 3 redness and swelling was less than 5% following each dose.*

The maximum redness reported was 20.0 cm in a 79 YO man with CLL receiving vaccination during cancer therapy, which was resolved post-vaccination day 5 following dose 2 of HZ/su. The maximum swelling reported was 17.0 cm in a 58 YO man with CLL receiving vaccination during cancer therapy, which had resolved the following day, post-vaccination day 3 after dose 2 of HZ/su. Nine subjects in the HZ/su group and one subject in the placebo group reported unsolicited AEs of local injection site reactions. In the HZ/su group this included injection site pruritis, bruising, pain, warmth, and movement impairment. Three of these subjects reported

these events as severe, including two subjects with injection site pruritus and one with injection site movement impairment. Each injection site unsolicited AE resolved within 10 days or less.

The proportions of subjects in each treatment group reporting individual local symptoms (any grade and Grade 3) overall by age strata with both doses considered are presented below.

Table 48. Incidence of solicited local symptoms reported during the 7-day post-vaccination period overall by subject, both doses considered, by age strata, Zoster-039 (TVC)

Solicited Symptom	Grade	HZ/su 18 – 49 YOA N=74 n (%)	Placebo 18 – 49 YOA N=71 n (%)	HZ/su ≥50 YOA N=204 n (%)	Placebo ≥50 YOA N=203 n (%)
Pain	All	67 (90.5)	13 (18.3)	154 (75.5)	32 (15.8)
	Grade 3	9 (12.2)	0 (0)	20 (9.8)	0 (0)
Redness (mm)	Any grade	30 (40.5)	2 (2.8)	85 (41.7)	3 (1.5)
	>100	2 (2.7)	0 (0)	10 (4.9)	0 (0)
Swelling (mm)	Any grade	20 (27.0)	0 (0)	43 (21.1)	2 (1.0)
	>100	1 (1.4)	0 (0)	4 (2.0)	0 (0)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 10.50, pp. 988 - 989
TVC = total vaccinated cohort; YOA = years of age; N = number of subjects with at least one documented dose; n (%) = number / percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
Any grade redness and swelling includes subjects with events measured ≥20 mm, or reported as present with missing measurements

Reviewer comment: *By age strata presented, in this population with hematologic malignancies, more subjects in the younger age stratum reported pain and slightly more subjects reported swelling compared to the older age stratum. In the autoHCT population enrolled in Zoster-002, similar proportions of subjects in the HZ/su groups reported each individual local solicited symptom in the younger and older age strata. Grade 3 local solicited symptoms were reported with similar frequency in both age strata. Although not shown here, in the younger age stratum, reports of any redness tended to increase following dose 2 (33.8%) compared to dose 1 (24.3%). In the older age stratum, reports of Grade 3 pain (3.9% and 9.1% following dose 1 and 2, respectively) and Grade 3 redness (0.5% and 4.8%, respectively) tended to increase with the second dose.*

The Applicant presented solicited local symptoms by underlying diagnosis (MM and 'other diagnoses', CLL, and NHBCL) and timing of vaccination with respect to immunosuppressive cancer therapy (before or after cancer therapy. Trends in these groups were similar to that presented above.

Overall per dose, the mean (median) duration of pain, redness or swelling reported after HZ/su administration was 3.2 (3.0), 3.5 (3.0) and 3.3 (3.0) days, respectively. For subjects who reported pain, redness, or swelling beyond the 7-day assessment period, the median number of days beyond the assessment period until resolution was 2.0 for swelling and 5.0 for pain and redness. The maximum duration of pain, redness, and swelling reported after HZ/su administration was 63, 59, and 51 days.

Solicited general symptoms: Overall by subject, at least one solicited general symptom was reported by 74.1% and 48.9% of subjects in the HZ/su group and placebo group, respectively and at least one Grade 3 solicited general symptom was reported 15.5% and 6.2% of subjects in the HZ/su and placebo groups, respectively. The numbers and proportions of subjects in the TVC reporting any grade and Grade 3 individual solicited general symptoms with both doses considered are below.

Table 49. Incidence of solicited general symptoms reported during the 7-day post-vaccination period overall by subject, both doses considered, Zoster-039 (TVC)

Solicited Symptom	Grade	HZ/su N	HZ/su n	HZ/su %	Placebo N	Placebo n	Placebo %
Fatigue	All	278	162	58.3	274	102	37.2
	Grade 3	278	23	8.3	274	10	3.6
Gastrointestinal symptoms	All	278	76	27.3	274	29	10.6
	Grade 3	278	9	3.2	274	3	1.1
Headache	All	278	115	41.4	274	64	23.4
	Grade 3	278	12	4.3	274	6	2.2
Myalgia	All	278	122	43.9	274	48	17.5
	Grade 3	278	22	7.9	274	5	1.8
Shivering	All	278	69	24.8	274	18	6.6
	Grade 3	278	11	4.0	274	0	0
Temperature	All*	278	68	24.5	274	21	7.7
	>39†	278	3	1.1	274	1	0.4
	>39.5†	278	1	0.4	274	0	0

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 36, pp. 212 – 216
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n/% = number / percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
* Fever defined as ≥37.5°C for oral, axillary, or tympanic route, or missing
† Temperature as assessed via oral, axillary, or tympanic route

Overall by subject, the most frequently reported general solicited symptoms reported by subjects in both the HZ/su and placebo groups were fatigue (58.3% and 37.2% of subjects, respectively), myalgia (43.9% and 17.5%, respectively), and headache (41.1% and 23.4%, respectively). The most frequently reported Grade 3 solicited general adverse events were fatigue and myalgia.

Reviewer comment: *All solicited general adverse events of any grade and Grade 3 events were reported more frequently in the HZ/su group compared to the placebo group. As in the autoHCT population, solicited general symptoms were common following HZ/su.*

The table below shows the number and proportion of subjects in the HZ/su group reporting any grade and Grade 3 individual solicited general symptoms following dose 1 and 2.

Table 50. Incidence of solicited general symptoms reported in the HZ/su group during the 7-day post-vaccination period following dose 1 and dose 2 overall by subject, Zoster-039 (TVC)

Solicited Symptom	Grade	Dose 1 N	Dose 1 n	Dose 1 %	Dose 2 N	Dose2 n	Dose2 %
Fatigue	All	278	122	43.9	255	126	49.4
	Grade 3	278	11	4.0	255	16	6.3
Gastrointestinal symptoms	All	278	48	17.3	255	53	20.8
	Grade 3	278	5	1.8	255	5	2.0
Headache	All	278	70	25.2	255	90	35.3
	Grade 3	278	3	1.1	255	10	3.9
Myalgia	All	278	80	28.8	255	93	36.5
	Grade 3	278	11	4.0	255	14	5.5
Shivering	All	278	39	14.0	255	48	18.8
	Grade 3	278	2	0.7	255	9	3.5

Solicited Symptom	Grade	Dose 1 N	Dose 1 n	Dose 1 %	Dose 2 N	Dose2 n	Dose2 %
Temperature	All*	278	33	11.9	255	51	20.0
	>39†	278	0	0	255	3	1.2
	>39.5†	278	0	0	255	1	0.4

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 36, pp. 212 – 216
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n/% = number / percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
* Fever defined as ≥37.5°C for oral, axillary, or tympanic route, or missing
† Temperature as assessed via oral, axillary, or tympanic route

Reviewer comment: *All individual solicited general symptoms tended to be reported by subjects in the HZ/su group at slightly increased frequency following dose 2 compared to dose 1.* The Applicant did not specify a Grade 4 for solicited AEs in their protocol. No fevers >40°C (Grade 4 as suggested by FDA guidance) were reported (Food and Drug Administration 2007).

The proportions of subjects in each treatment group reporting individual general symptoms (any grade and Grade 3) overall by age strata with both doses considered are presented below.

Table 51. Incidence of solicited general symptoms reported during the 7-day post-vaccination period overall by subject, both doses considered, by age strata, Zoster-039 (TVC)

Solicited Symptom	Grade	HZ/su 18 – 49 YOA N=74 n (%)	Placebo 18 – 49 YOA N=71 n (%)	HZ/su ≥50 YOA N=204 n (%)	Placebo ≥50 YOA N=203 n (%)
Fatigue	All	44 (59.5)	30 (42.3)	118 (57.8)	72 (35.5)
	Grade 3	9 (12.2)	1 (1.4)	14 (6.9)	9 (4.4)
Gastrointestinal symptoms	All	22 (29.7)	6 (8.5)	54 (26.5)	23 (11.3)
	Grade 3	3 (4.1)	1 (1.4)	6 (2.9)	2 (1.0)
Headache	All	37 (50.0)	17 (23.9)	78 (38.2)	47 (23.2)
	Grade 3	1 (1.4)	0 (0)	11 (5.4)	6 (3.0)
Myalgia	All	44 (59.5)	15 (21.1)	78 (38.2)	33 (16.3)
	Grade 3	8 (10.8)	3 (4.2)	14 (6.9)	2 (1.0)
Shivering	All	23 (31.1)	3 (4.2)	46 (22.5)	15 (7.4)
	Grade 3	3 (4.1)	0 (0)	8 (3.9)	0 (0)
Temperature	All*	24 (32.4)	4 (5.6)	44 (21.6)	17 (8.4)
	>39†	1 (1.4)	0 (0)	2 (1.0)	1 (0.5)
	>39.5†	0 (0)	0 (0)	1 (0.5)	0 (0)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 10.51, pp. 990 - 997
TVC = total vaccinated cohort; YOA = years of age; N = number of subjects with at least one documented dose; n (%) = number / percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
* Fever defined as ≥37.5°C for oral, axillary, or tympanic route, or missing.
† Temperature as assessed via oral, axillary, or tympanic route

Reviewer comment: *Any grade of myalgia was reported more frequently, and any grade of headache, myalgia, shivering, and fever tended to be reported more frequently following HZ/su in the younger age stratum compared to the older age stratum. Grade 3 fatigue also tended to be reported more frequently in the younger age stratum compared to the older age stratum. This is similar to the post-autoHCT population in Zoster-002 and the general older adult population in the original BLA. Overall by subject, Grade 3 events reported by ≥5% of HZ/su subjects in a single age stratum with both doses considered were fatigue (12.2%) and myalgia (10.8%) in the 18 – 49 YOA group and fatigue (6.9%), headache (5.4%), and myalgia (6.9%) in the ≥ YOA group.*

Although not shown here, in both age strata, in general the proportion of subjects reporting individual solicited symptoms increased following dose 2 compared to dose 1. One exception is that shivering did not increase in the ≥50 YOA stratum with a second dose, but it increased in the 18 – 49 YOA stratum following dose 2 compared to dose 1. For the 18 – 49 YOA stratum, grade 3 fatigue increased following dose 2 compared to dose 1 and for the ≥50 YOA stratum, grade 3 headache increased following dose 2 compared to dose 1. Similar to Zoster-002, fever was common following HZ/su, particularly in subject 18 – 49 YOA (32.4%), with an increase in the proportion of subjects reporting fever following dose 2 compared to dose 1. High fever (>39°C) was infrequent in both strata after any dose. Fever is a pertinent finding in this population that may have a low threshold for initiating diagnostic tests and empiric therapies.

The Applicant presented solicited general symptoms by underlying diagnosis (MM and 'other diagnoses', CLL, and NHBCL) and timing of vaccination with respect to immunosuppressive cancer therapy (during or after cancer therapy). Trends in these groups were similar to those presented for the entire study population.

Overall per dose, the mean (median) duration of fatigue, GI symptoms, headache, myalgia, shivering and fever reported after HZ/su administration was 7.2 (3.0), 5.7 (2.0), 2.6 (2.0), 3.6 (3.0), 2.4 (2.0), and 1.8 (1.0) days, respectively. Myalgia duration was longer following dose 1 [4.2 (3.5)] compared to dose 2 [3.1 (2.0)] in subjects who received HZ/su. There were no other notable differences in median duration of solicited general symptoms following dose 1 and dose 2.

Reviewer comment: *A majority of solicited general symptoms were of limited duration. Some reports of extended duration of solicited general symptoms may be more reflective of the study population, as they were reported in both the HZ/su and the placebo groups.*

Unsolicited Adverse Events

Unsolicited AEs were recorded by all subjects on a diary card for 30 days (Days 0 – 29) after each vaccination.

Overall by subject, 47.3% and 45.9% of subjects in the TVC of the HZ/su and placebo groups, respectively, reported at least one unsolicited (serious or non-serious) AE in the 30-day post-vaccination period. The most frequently reported unsolicited AEs by PT in the HZ/su group were:

- nausea (11 subjects, 3.9% in the HZ/su and 6 subjects, 2.2% in the placebo groups),
- pyrexia (10 subjects, 3.5% in the HZ/su and 5 subjects, 1.8% in the placebo groups),
- oropharyngeal pain (10 subjects, 3.5% in the HZ/su and 3 subjects, 1.1% in the placebo groups),
- cough (9 subjects, 3.2% in the HZ/su and 10 subjects, 3.6% in the placebo groups),
- diarrhea (9 subjects, 3.2% in the HZ/su and 5 subjects, 1.8% in the placebo groups), and
- upper respiratory tract infection (9 subjects, 3.2% in the HZ/su and 1 subject, 0.4% in the placebo groups).

The most frequently reported unsolicited AEs by PT in the placebo group were cough (see above) and nasopharyngitis (7 subjects, 2.5% in the HZ/su and 9 subjects, 3.2% in the placebo groups).

Reviewer comment: *Overall the proportion of subjects reporting any unsolicited adverse events occurring in the month after vaccination were balanced between treatment groups.*

Although upper respiratory tract infection was reported more frequently in the HZ/su group, the HLT of Upper respiratory tract infections, including similar terms, was balanced between vaccine groups (22 subjects, 7.8% in the HZ/su and 18 subjects, 6.5% in the placebo groups).

The table below shows the unsolicited AEs that were reported in at least 1% in the HZ/su group and 1.5 times the proportion of subjects reporting in the placebo group.

Table 52. Unsolicited Adverse Events reported within the 30-day post-vaccination period in at least 1% of subjects in the HZ/su group and at ≥1.5 times the proportion of subjects reporting those events in the placebo group, Zoster-039 (TVC)

Unsolicited AE Preferred Term	HZ/su N=283 n	HZ/su N=283 %	Placebo N=279 n	Placebo N=279 %
Nausea	11	3.9	6	2.2
Oropharyngeal pain	10	3.5	3	1.1
Pyrexia	10	3.5	5	1.8
Diarrhea	9	3.2	5	1.8
Upper respiratory tract infection	9	3.2	1	0.4
Febrile neutropenia	8	2.8	2	0.7
Back pain	7	2.5	3	1.1
Arthralgia	5	1.8	3	1.1
Decreased appetite	5	1.8	2	0.7
Headache	4	1.4	2	0.7
Injection site pruritus	4	1.4	0	0
Pain in extremity	4	1.4	1	0.4
Urinary tract infection	4	1.4	1	0.4
Catheter site infection	3	1.1	0	0
Conjunctivitis	3	1.1	0	0
Depression	3	1.1	0	0
Dyspnea	3	1.1	1	0.4
Ear infection	3	1.1	0	0
Eczema	3	1.1	0	0
Erythema	3	1.1	1	0.4
Malaise	3	1.1	1	0.4
Sinusitis	3	1.1	1	0.4

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 10.20, pp. 921 – 930.
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n (%) = number / percentage of subjects reporting the symptom

Reviewer comment: *A smaller number of subjects compared to Zoster-002, were enrolled, contributing to more events meeting the criteria of >1% in the HZ/su group used above. Of note, Infective pneumonia was reported more frequently in Zoster-002 in the HZ/su group (1.8% in the HZ/su and 1.1% in the placebo groups). In Zoster-039, 4 subjects in each group (1.4%) reported an unsolicited AE in the 30-day post-vaccination period with a PT in the SMQ Infective pneumonia.*

Pyrexia and febrile neutropenia are pertinent to subjects with hematologic malignancies and were observed more frequently in the HZ/su group. In the HZ/su group 10 subjects reported 12 events of pyrexia in the 30-day post-vaccination period, reported as starting from 7 to 28 days following vaccination. All but one of these events occurred 14 days or more after vaccination. None of these events were serious and all were mild to moderate (one event was missing severity). None of the events in the HZ/su group were assessed by investigators as related to

vaccine. Please also see the summary of the solicited AE of fever within seven days post-vaccination, which was more common in the HZ/su group.

In the HZ/su group, 9 events of febrile neutropenia were reported in eight subjects. Seven of the eight subjects were vaccinated during receipt of cancer therapy. The events were reported as starting 9 to 29 days following vaccination, with all but one event beginning more than 14 days after vaccination. Six subjects had events that were serious. None of the events were assessed by investigators as related to vaccine. The SMQ *Agranulocytosis*, which includes Febrile neutropenia and pancytopenia, also showed a numerical imbalance due to the imbalance in Febrile neutropenia. The sub-SMQ *Hematopoietic leukopenias*, which includes febrile neutropenia, neutropenia, and laboratory investigations indicative of leukopenia, was balanced between treatment groups (12 subjects, 4.2% in the HZ/su and 11 subjects, 3.9% in the placebo groups).

Reviewer comment: *Unsolicited AEs of neutropenia (febrile or not) appeared to be well-balanced between groups, suggesting the vaccine did not contribute to the neutropenia. It is possible vaccination contributed to the numerical imbalance in febrile neutropenia by contributing to an imbalance in fever in neutropenic subjects. However, almost all of these events of febrile neutropenia in HZ/su recipients occurred more than 2 weeks following vaccination, making a vaccine-associated fever less likely. In the older adult trials submitted with the original BLA, a between-group difference in fever occurred within 3 days post-vaccination, and no clinically significant between-group differences were observed in fever with onset 7 through 29 days post-vaccination. Furthermore, investigators did not assess any of the events of fever or febrile neutropenia in the vaccine group as related, suggesting there were other explanations for the events. The Applicant also notes that the majority of subjects reporting febrile neutropenia received chemotherapy within the 15 days prior to the onset of the neutropenia; however, a similar number of subjects in the placebo as the HZ/su group were vaccinated during their chemotherapy course.*

Numerical imbalances were also noted in CBER SMQ analyses in the SMQ *Hemorrhages* (8 subjects, 2.8% in the HZ/su and 1 subject, 0.4% in the placebo groups) and the sub-SMQ *Gastrointestinal nonspecific symptoms and therapeutic procedures* (27 subjects, 9.5% in the HZ/su and 16 subjects, 5.7% in the placebo groups). PTs in the SMQ *Hemorrhages* represented a variety of disorders, including injection site and other bruising, retinal and conjunctival hemorrhage, epistaxis, hematochezia, and hemoptysis. When considering medically attended Hemorrhages, the imbalance was diminished (5 of the subjects in the HZ/su group and one subject in the placebo group). One of the subjects who received HZ/su and reported a PT in the SMQ *Hemorrhage* (PT = retinal hemorrhage) had a concurrent thrombocytopenia. However, the sub-SMQ *Hematopoietic thrombocytopenias* was balanced between vaccine groups (3 subjects in each group, 1.1%). The difference in the sub-SMQ *Gastrointestinal nonspecific symptoms and therapeutic procedures* can be mostly attributed to differences between vaccine groups in the PTs of nausea and diarrhea.

There were also numerical imbalances in the SOC General disorders and administration site conditions (36 subjects, 12.7% in the HZ/su and 23 subjects, 8.2% in the placebo groups), Respiratory, thoracic and mediastinal disorders (23 subjects, 8.1% in the HZ/su and 14 subjects, 5.0% in the placebo groups), and Ear and labyrinth disorders (5 subjects, 1.8% in the HZ/su and 0 subjects in the placebo groups). Of note, an imbalance in the opposite direction was noted in the SOC Neoplasms benign, malignant and unspecified (6 subjects, 2.1% in the HZ/su and 22 subjects, 7.9% in the placebo groups). The between-group difference in the SOC General disorders was due to numerical imbalances in pyrexia, as well as injection site

reactions and fatigue/malaise. The between-group difference in the SOC Respiratory, thoracic and mediastinal disorders was largely attributable to the difference in oropharyngeal pain ("sore throat"). PTs in the SOC Ear and labyrinth disorders included ear pain (2 subjects in the HZ/su group), tinnitus (2 subjects in the HZ/su group), and eustachian tube dysfunction (1 subject in the HZ/su group), all mild to moderate. Although one event each of ear pain and tinnitus started the day after dose 1, all events were assessed by investigators as unrelated.

Reviewer comment: *Although some numerical imbalances in specific unsolicited AEs reported in the 30-day post-vaccination period were observed, there is no clinically significant imbalance the reviewer identified likely attributable to the vaccine.*

At least one Grade 3 non-serious unsolicited AE was reported by 17 (6.0%) subjects in the HZ/su group and 14 (5.0%) subjects in the placebo group within the 30-day post-vaccination period. The only PTs reported in more than one subject were arthralgia (2 subjects, 0.7% in the HZ/su and 0 subjects in the placebo groups) and injection site pruritus (2 subjects, 0.7% in the HZ/su and 0 subjects in the placebo groups) in the HZ/su group and neutropenia (0 subjects in the HZ/su and 3 subjects, 1.1% in the placebo groups), and AML (0 subjects in the HZ/su and 2 subjects, 0.7% in the placebo groups).

Reviewer comment: *Of note, grade 3 neutropenia was reported more frequently in the HZ/su group in Zoster-002, but more frequently in the placebo group in Zoster-039.*

Overall by subject, 19 (6.7%) subjects in the HZ/su group and 5 (1.8%) subjects in the placebo group reported at least one unsolicited AE within the 30-day post-vaccination period assessed by the investigator as related to vaccination. The most frequently reported terms in the HZ/su group were injection site reactions, including pruritus, bruising, movement impairment, pain and warmth (9 subjects in the HZ/su and 1 subject in the placebo groups), malaise (2 subjects in the HZ/su and 0 subjects in the placebo groups), and arthralgia (2 subjects in the HZ/su and 0 subjects in the placebo groups). Other select PTs reported in one subject in the HZ/su group and no subjects in the placebo group assessed as related by the investigators were cardiac flutter and C-reactive protein (CRP) increased. The cardiac flutter was moderate, not medically attended, reported on the day of the first vaccination of one day duration, and was not reported after the second vaccination. The "CRP increased" was mild, not medically attended, reported starting 4 days post-dose 1 and unresolved. This subject was discontinued from receiving the second vaccination with a reason of "Other" and "Per Protocol, patient was under immunosuppression," noted in the datasets.

Reviewer comment: *An imbalance in related events was due primarily to IS reactions and other symptoms similar to solicited AEs. The other two noted events appear to be isolated events in a single individual, the etiologies of which are difficult to attribute to HZ/su.*

Five subjects, all in the HZ/su group (1.8%), reported grade 3 nonserious AEs assessed as related within the 30-day post-vaccination period. The PTs were injection site pruritus (2 subjects), injection site movement impairment, pain in extremity (right arm), and one subject with asthenia and arthralgia. All resolved within 6 days or less except pain in extremity, for which a 45-day duration was reported.

Unsolicited AEs by subgroups: In the 18 – 49 YOA group, unsolicited AEs (serious and non-serious) in the 30-day period following vaccination were reported by 30 subjects (40.5%) in the HZ/su group compared to 26 subjects (35.6%) in the placebo group. In the 18 – 49 YOA group, Grade 3 non-serious unsolicited AEs were reported by 4 subjects (5.4%) in the HZ/su group

compared to 1 subject (1.4%) in the placebo group. In the 18 – 49 YOA, unsolicited AEs (serious and non-serious) assessed as related were reported by 5 subjects (6.8%) following HZ/su and 0 subjects following placebo. Related unsolicited AE PTs in this age stratum were Malaise and Back pain in one subject, Injection site pruritus, CRP increased, Pain in extremity, and Paresthesia. For the ≥50 YOA group, a similar proportion of subjects reported unsolicited AEs and Grade 3 non-serious unsolicited AEs in the 30-day period following HZ/su compared to following placebo. In the ≥50 YOA stratum, 14 subjects (6.7%) in the HZ/su group and 5 subjects (2.4%) in the placebo group reported unsolicited AEs assessed as related. In the HZ/su group, a majority of unsolicited AEs assessed as related were injection site or solicited reactions.

Reviewer comment: *There was a trend in the 18 – 49 YOA stratum toward a greater proportion HZ/su recipients reporting unsolicited AEs within the 30-day post-vaccination period compared to placebo recipients. No clinically significant differences by PT were identified in the unsolicited AEs reported in this age stratum. The number of subjects enrolled in this age stratum was low.*

The Applicant presented the unsolicited AEs by underlying disease and timing of vaccination with respect to chemotherapy. The proportions of subjects reporting unsolicited AEs in the 30-day post-vaccination period was similar between the HZ/su and placebo groups within each subgroup.

Medically Attended Adverse Events (MAAEs)
MAAEs were analyzed for the reporting period for unsolicited AEs, the 30-day post-vaccination period following each vaccination.

Overall, 83 (29.3%) subjects in the HZ/su group and 86 (30.8%) subjects in the placebo group reported at least one unsolicited AE with a medically attended visit within 30 days post-vaccination. The SOCs with the highest proportions of subjects reporting events were Infections and infestations (with 13.8% and 11.1% of HZ/su and placebo recipients reporting events, respectively) and the Gastrointestinal disorders (with 7.8% and 5.4% of HZ/su and placebo recipients reporting events, respectively). The most frequently reported MAAEs in the HZ/su group were febrile neutropenia (8 subjects, 2.8% in the HZ/su and 2 subjects, 0.7% in the placebo groups), nausea (8 subjects, 2.8% in the HZ/su and 3 subjects, 1.1% in the placebo groups), and pyrexia (6 subjects, 2.1% in the HZ/su and 3 subjects, 1.1% in the placebo groups). The most frequently reported MAAEs in the placebo group were AML (1 subject, 0.4% in the HZ/su group and 8 subjects, 2.9% in the placebo group), cough (5 subjects, 1.8% in the HZ/su and 4 subjects, 1.4% in the placebo group), and neutropenia (3 subjects, 1.1% in the HZ/su and 4 subjects, 1.4% in the placebo groups).

Reviewer comment: *No patterns of imbalance were observed between treatment groups except those noted elsewhere (see SAEs of pneumonia below).*

The proportions of subjects reporting MAAEs between the HZ/su and placebo group within each age, disease, and timing of vaccination with regard to cancer therapy strata were generally similar.

6.2.12.3 Deaths

A summary of subjects in the TVC with fatal SAEs (who died) during select time periods by treatment group is below.

Table 53. Subjects who died during selected time periods, Zoster-039 (TVC)

	HZ/su N=283 n (%)	Placebo N=279 n (%)
Subjects who died Days 0 – 29 post-vaccination	0 (0)	2 (0.7)
Subjects who died Day 0 – Month 13 (365 days after last vaccination)	25 (8.8)*	33 (11.8)
Subjects with fatal SAE reported Day 0 through study end	29 (10.2)*	37 (13.3)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 10.251, p. 1475; and Table 10.252, pp. 1476 - 1478
TVC = total vaccinated cohort; N = number of subjects with at least one documented dose; n (%) = number / percentage of subjects reporting the symptom or the symptom of Grade 3 at least once
* Includes one neonatal death in the child of a subject who received HZ/su

SAEs, including fatal SAEs, were collected and reported through study end, 12 months following the last dose, with an allowed a visit interval of 335 to 425 days post-last vaccination. There were several events in the datasets reported beyond 425 days following vaccination. As reporting of events beyond Visit 4/M13 was not pre-specified, CBER requested the Applicant submit a summary of deaths, SAEs, and disease-related events through 365 days post-vaccination. The 365-day post-vaccination time period will be the focus of the data presented in this document.

One fatal SAE (Neonatal death) occurred in a neonate of a subject who received the second dose of HZ/su 34 days before her last menstrual period. The fatal SAE was reported 307 days after the second dose of HZ/su and was assessed by the investigator as related to vaccination. This event is included in the fatal SAE, SAE, and related SAE summaries. Please see section 9.1.1 for additional details on this event.

Reviewer comment: *There were no clinically significant differences between treatment groups in the proportions of subjects who died within the above time periods.*

Fatal SAEs with death occurring through 30 days following the last vaccination: No subjects in the HZ/su group and two subjects in the placebo group died within 30 days following the last vaccination.

Fatal SAEs with death occurring through 365 days following the last vaccination: 25 subjects in the HZ/su group (8.8%) and 33 subjects in the placebo group (11.8%) died through one year following the last vaccination. The greatest number of fatal SAEs had PTs belonging to the SOC Infections and infestations (11 subjects, 3.9% in the HZ/su and 8 subjects, 2.9% in the placebo groups) and Neoplasms benign, malignant and unspecified (10 subjects, 3.5% in the HZ/su and 19 subjects, 6.8% in the placebo groups). PTs of fatal SAEs reported in more than one subject in the HZ/su group included Pneumonia (3 subjects in the HZ/su and 4 subjects in the placebo groups), Hodgkin's disease (2 subjects in the HZ/su and 1 subject in the placebo groups), Respiratory failure (2 subjects in the HZ/su and 1 subject in the placebo groups), and the following PTs reported in 2 subjects each in the HZ/su group and no subjects in the placebo group: ALL, Hepatitis B, Septic shock, and Thrombocytopenia. Fatal SAEs with PTs in the SMQs *Sepsis* and *Shock* were reported in the same number or more subjects in the placebo group compared to the HZ/su group.

With regard to the fatal events of thrombocytopenia, one event began six days post-dose 2 in the setting of a relapse of the subject's AML (also listed as fatal) and the other event began 49 days post-dose 2 and in the setting of recurrent myelodysplastic syndrome (ongoing prior to study enrollment), chronic neutropenia, and multiple systemic infections. With regard to the fatal events of Hepatitis B, both subjects were in the subgroup vaccinated during cancer therapy that

could result in hepatitis B reactivation (for example, rituximab, bendamustine). One of the subjects had a documented history of chronic hepatitis B and was not receiving antiviral therapy at study enrollment until 16 days prior to the SAE of hepatitis B.

Reviewer comment: *The proportion of subjects and types of fatal SAEs were generally similar between groups.*

Fatal SAEs during the entire study: During this period, 29 (10.2%) and 37 (13.3%) subjects died in the HZ/su and placebo groups, respectively. There were 8 additional deaths, 4 in each treatment group reported greater than 365 days after the last dose. Each of these subjects had a progression or relapse of their hematologic malignancy reported as one of the events contributing to a fatal outcome.

Related fatal SAEs: No fatal SAEs were assessed as related to vaccination by the investigator throughout the entire study period, with the exception of one neonatal death in a neonate born to a subject who received HZ/su (see section 9.1.1).

Fatal SAEs by subgroups: The proportions of subjects who died in each vaccine group was higher in the older age stratum. During the one-year post-vaccination period, a similar proportion of subjects in the HZ/su and the placebo groups died in the 18 – 49 YOA stratum (1 subject, 1.4% and 4 subjects, 5.5%, respectively) and in the ≥50 YOA group (23 subjects, 11.0% and 29 subjects, 14.1%, respectively). The HZ/su recipient who died in the 18 – 49 YOA group died of their underlying malignancy. An additional subject who received HZ/su reported a fatal SAE of Neonatal death of her child that is classified as a death in the Zoster-039 CSR (see brief information above and details in section 9.1.1).

Reviewer comment: *No clinically significant differences in deaths were identified by age strata.*

The Applicant presented fatal SAEs by underlying disease and timing of vaccination with respect to cancer therapy. The proportion of subjects who died by underlying disease and timing with respect to cancer therapy was similar between vaccination groups.

6.2.12.4 Nonfatal Serious Adverse Events

The Applicant included both fatal and non-fatal SAEs in their tabulations of SAEs.

All SAEs were monitored through the one-year post-vaccination visit. A secondary endpoint included SAEs occurring from the first vaccination up to 6 months post-last vaccination in at least 50% of the TVC; therefore, a tabulation of SAEs in all subjects at that time point is presented below. A summary of SAEs occurring up to 30 days and up to 365 days following the last vaccination is the focus of this review for reasons stated above.

Table 54. Summary of SAEs up to 30 days, 6 months (182 days), and one year (365 days) post-last vaccination, Zoster-039 (TVC)

	HZ/su N=283 n (%)	Placebo N=279 n (%)
Subjects with at least one SAE reported up to 30 days post-last vaccination	17 (6.0)	29 (10.4)
Subjects with at least one SAE reported up to 6 months (182 days) post-last vaccination	50 (17.7)	60 (21.5)
Subjects with at least one SAE reported up to 365 days post-last vaccination	66 (23.3)	81 (29.0)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 41, p. 221; and Table 42, p. 221
SAE = serious adverse event; TVC = total vaccinated cohort; N = number of subjects with at least one administered dose; n (%) = number / percentage reporting the symptom

Reviewer comment: *Overall by subject, the proportion of subjects who reported SAEs within one month, six months, and one year of last vaccination were similar between treatment groups. A reviewer conducted analysis excluding SAEs related to HZ (three SAEs in two placebo recipients) did not alter the numbers presented above.*

Up to 30 days post-last vaccination, the SOCs with more than one subject in the HZ/su group reporting SAEs were Infections and infestations (9 subjects, 3.2% in the HZ/su and 8 subjects, 2.9% in the placebo group), Blood and lymphatic system disorders (8 subjects, 2.9% in the HZ/su group and 4 subjects, 1.4% in the placebo groups), and Neoplasms benign, malignant and unspecified (2 subjects, 0.7% in the HZ/su and 9 subjects, 3.2% in the placebo groups). The only PTs with more than one reported SAE in the HZ/su group were Febrile neutropenia (7 subjects, 2.5% in the HZ/su and 2 subjects, 0.7% in the placebo groups) and Pneumonia (5 subjects, 1.8% in the HZ/su group and 0 subjects in the placebo groups). The PTs with more than one reported SAE in the placebo group were AML (1 subjects, 0.4% in the HZ/su and 3 subjects, 1.1% in the placebo groups), Plasma cell myeloma (1 subject, 0.4% in the HZ/su and 3 subjects, 1.1% in the placebo groups), Febrile neutropenia (see above), and Respiratory tract infection (1 subject, 0.4% in the HZ/su and 2 subjects, 0.7% in the placebo groups). A CBER analysis demonstrated that the SMQ *Infective pneumonia*, (6 subjects, 2.1% in the HZ/su and 1 subject, 0.4% in the placebo groups) was among the most frequently reported SMQs. The Narrow SMQs that contain Febrile neutropenia are *Agranulocytosis* (8 subjects, 2.8% in the HZ/su and 2 subjects, 0.7% in the placebo groups), which includes an additional subject with Pancytopenia in the HZ/su group, and the sub-SMQ *Hematopoietic leukopenias* (7 subjects, 2.5% in the HZ/su and 3 subjects, 1.1%), which includes an additional subject in the placebo group with Neutropenia.

Reviewer comment: *Up to 30 days post-last vaccination, there were numerical imbalances in the most frequently reported SAEs, Febrile neutropenia and Pneumonia, with more subjects reporting events in the vaccine group. Please see the discussion of unsolicited AEs (serious and non-serious) of febrile neutropenia in section 6.2.12.2. Although SAEs in the SMQ* Infective pneumonias *were imbalanced during the 30-day post-vaccination period, unsolicited AEs (including serious and non-serious events) in this Narrow SMQ were balanced (see section 6.2.12.2). SAEs in the SOC of Infections and Infestations is also balanced. In the HZ/su group, one SAE of pneumonia occurred 6 days post-vaccination, one event occurred 8 days post-vaccination and the remainder of events occurred 21 days or more following vaccination. This is in contrast to the imbalance in pneumonia seen in Zoster-002, which occurred predominantly in the first two weeks post-vaccination. Numbers of subjects reporting these specific adverse events were small, but a causal relationship with vaccination can't be ruled out.*

In the one-year post-vaccination period, the most frequently reported SAEs by PT in both the HZ/su and placebo groups were Febrile neutropenia (14 subjects, 4.9% in the HZ/su and 11 subjects, 3.9% in the placebo groups) and Pneumonia (10 subjects, 3.5% in the HZ/su and 11 subjects, 3.9% in the placebo groups. The SOCs with the greatest proportions of subjects reporting SAEs were Infections and infestations (39 subjects, 13.8% in the HZ/su and 34 subjects, 12.2% in the placebo groups), Neoplasms benign, malignant and unspecified (17 subjects, 6.0% in the HZ/su groups and 30 subjects, 10.8% in the placebo groups), and Blood and lymphatic system disorders (17 subjects, 6.1% in the HZ/su and 16 subjects, 5.7% in the placebo groups). The SMQ *Infective pneumonia*, containing the PT pneumonia, (17 subjects, 6.0% in the HZ/su and 16 subjects, 5.7% in the placebo groups) and the SMQs containing febrile neutropenia, *Agranulocytosis* (16 subjects, 5.7% in the HZ/su group and 12 subjects, 4.3% in the placebo groups) and the sub-SMQ *Hematopoietic leukopenia*s (16 subjects, 5.7% in the HZ/su group and 13 subjects, 4.7% in the placebo groups) were among the most frequently reported SMQs.

Reviewer comment: *The numerical differences in SAEs with a PT in the SMQ* Infective pneumonia *and with PTs of Febrile neutropenia diminished over time. A similar number of subjects in both vaccination groups died due to pneumonia (had a fatal SAE with a PT in the SMQ Infective pneumonia) up to 365 days post-last vaccination (4 subjects in the HZ/su and 5 subjects in the placebo groups). No clinically significant imbalances in SAEs up to 365 days were identified.*

SAEs by subgroups:
The proportions of subjects in each age stratum reporting at least one SAE during select time periods post-vaccination is below.

Table 55. Subjects reporting the occurrence of SAEs up to 30 days and 365 days post-last vaccination by age strata, Zoster-039 (TVC)

	HZ/su 18 – 49 YOA N=74 n (%)	Placebo 18 – 49 YOA N=73 n (%)	HZ/su ≥50 YOA N=209 n (%)	Placebo ≥50 YOA N=206 n (%)
Subjects with at least one SAE reported up to 30 days post-last vaccination	2 (2.7)	4 (5.5)	15 (7.2)	25 (12.1)
Subjects with at least one SAE reported up to 365 days post-last vaccination*	11 (14.9)	15 (20.5)	55 (26.3)	66 (32.0)
Subjects with at least one SAE reported up to study end	11 (14.9)	16 (21.9)	55 (26.3)	66 (32.0)

Source: Adapted from 125614/398.0, Zoster-039 CSR, Table 10.80, pp. 1068 – 1070; and Table 10.84, pp. 1072 – 1080
SAE = serious adverse event; TVC = total vaccinated cohort; N = number of subjects with at least one administered dose; n (%) = number / percentage reporting the symptom
* CBER-generated analysis

Within both age strata, a similar or lower proportion of subjects in the HZ/su group compared to the placebo group reported SAEs at the evaluated time points. The two subjects with SAEs in the HZ/su group in the 18 – 49 YOA stratum up to 30 days following the last vaccination reported Febrile neutropenia and Corynebacterium bacteremia in one subject and Pneumonia in the other. One subject in the placebo group reported an SAE of Respiratory tract infection during this time.

Reviewer comment: *With regard to the numerical imbalances in SAEs of Pneumonia and Febrile neutropenia up to 30 days post-vaccination noted previously, a majority of those events*

occurred in the ≥50 YOA stratum. No other clinically significant differences were identified within each age stratum by PT.

The Applicant presented SAEs by underlying disease and timing of vaccination with respect to cancer therapy. Most of the SAEs of Febrile neutropenia and Pneumonia up to 30 days following the last vaccination were reported in the 'MM and other diagnoses' stratum; however, this was the largest subgroup. Most of the SAEs of Febrile neutropenia and Pneumonia up to 30 days following the last vaccination were reported in subjects vaccinated during cancer therapy (instead of after cancer therapy); this subgroup has a greater risk of neutropenia and infection.

Related SAEs: The investigators assessed two SAEs as related to vaccination, one in each vaccination group (0.4%). The SAE assessed as related in HZ/su recipient was Neonatal death in the offspring of a subject (see brief information in 6.2.12.3 and details in section 9.1.1). The SAE assessed as related in the placebo group was Guillain-Barré syndrome.

6.2.12.5 Adverse Events of Special Interest (AESI)

Potential immune-mediated diseases (pIMDs): pIMDs were collected for the one-year post-vaccination period. The number and proportion of subjects reporting pIMDs at different time points by vaccination group is below.

Table 56. Subjects reporting the occurrence of pIMDs at selected time points, Zoster-039 (TVC)

	HZ/su N=283 n (%)	Placebo N=279 n (%)
Subjects with at least one pIMD reported up to 30 days post-last vaccination	1 (0.4)	0 (0)
Subjects with at least one pIMD reported up to 6 months post-last vaccination	3 (1.1)	1 (0.4)
Subjects with at least one pIMD reported up to 365 days post-last vaccination	3 (1.1)	2 (0.7)

Source: Adapted from 125614/398.0, CSR Table 44, p. 224; and Table 46, p. 225
pIMD = potential immune-mediated disease; TVC = total vaccinated cohort; N = number of subjects with at least one administered dose; n (%) = number / percentage reporting the symptom

Up to 30 days post-last vaccination, at least one pIMD was reported in 1 subject (0.4%) in the HZ/su group. This pIMD was gout and was identified in the Applicant's database search. Up to 365 days post-last vaccination, 3 (1.1%) HZ/su recipients and 2 (0.7%) placebo recipients reported at least one pIMD. The additional pIMDs in the HZ/su group were autoimmune pancytopenia and erythema nodosum. In the placebo group the reported pIMDs were autoimmune hemolytic anemia (AIHA) and Guillain-Barré syndrome.

Two pIMDs were assessed as serious and included in the SAE tabulations above – Erythema nodosum in the HZ/su group and Guillain-Barré syndrome in the placebo group. No pIMDs in the HZ/su group were considered related to vaccination by investigators. One pIMD, Guillain-Barré syndrome, in the placebo group was assessed as related.

Reviewer comment: *See CBER analysis of pIMD reporting over all studies in section 8.4.8.*

Disease-related events: Disease-related events were defined as 1) Progression of the hematologic malignancy and 2) Relapse of the hematologic malignancy. They were collected through the study end and were specifically identified as disease-related events by

investigators. The number and proportion of subjects reporting events of relapse at different time points by vaccination group is below.

Table 57. Subjects reporting the occurrence of relapse at selected time points, Zoster-039 (TVC)

	HZ/su N=283 n (%)	Placebo N=279 n (%)
Subjects with at least one relapse reported up to 30 days post-last vaccination	6 (2.1)	19 (6.8)
Subjects with at least one relapse reported up to 365 days post-last vaccination	45 (15.9)	57 (20.4)
Subjects with at least one relapse reported through study end	45 (15.9)	58 (20.8)

Source: Adapted from 125614/398.0, Zoster-039 CSR Table 10.36, p. 967; and 10.37, pp. 968 – 970
TVC = total vaccinated cohort; N = number of subjects with at least one administered dose; n (%) = number/percentage reporting the symptom

Reviewer comment: *The proportions of subjects reporting disease-related events as determined by investigators were similar at the specified time points. There were not clinically significant differences observed in the proportions of subjects who reported disease-related events by age stratum, underlying disease subgroup, or timing of vaccination related to cancer therapy.*

6.2.12.6 Clinical Test Results

Not applicable.

6.2.12.7 Dropouts and/or Discontinuations

Please see section 6.2.10.1.3 for subject disposition. Five subjects (1 in the HZ/su group and 4 in the placebo group) were withdrawn from vaccination at Visit 2 due to a non-serious AE. The PT in the HZ/su group leading to withdraw from vaccination was Upper respiratory tract infection in a subject who also reported moderate pain (“general ache”) post-dose 1, assessed as related, and of 37 days duration. Twelve subjects (7 in the HZ/su group and 5 in the placebo group) did not complete Visit 2 due to a serious or non-serious AE. None of the non-serious AEs or SAEs leading to withdrawal from vaccination or inability to complete Visit 2/M1, hence leading to a withdrawal from vaccination, were assessed as related to vaccination.

Up to the study end, 19.6% of subjects (16.6% in the HZ/su and 22.6% in the placebo groups) were withdrawn. This includes 12.1% (10.3% in the HZ/su and 13.9% in the placebo groups) who were withdrawn for serious or non-serious AEs. None of the AEs leading to study withdrawal were assessed as related by investigators. At the time of Visit 3/M2, one month after the last vaccination, 6.6% of subjects had withdrawn.

Reviewer comment: *A similar or lower proportion of subjects in the HZ/su group compared to the placebo group were withdrawn from treatment and withdrawn from the study at the time points evaluated, as well as withdrawn due to SAEs and AEs. However, the high proportion of subjects withdrawn from the study after Visit 3 may have limited the collection of longer-term safety data in this study.*

6.2.13 Study Summary and Conclusions

Zoster-039 was an observer-blind, randomized, placebo-controlled trial to assess the safety and immunogenicity of two doses of HZ/su administered months 0 and 1-2 in adults diagnosed with a hematologic malignancy who had recently received (within 10 days to 6 months) or were currently receiving immunosuppressive cancer therapy.

The co-primary objectives evaluating VRR and GMC ratio of anti-gE Ab response in subjects without CLL and without NHBCL in HZ/su group compared to the placebo group were met. At study end, after one year of follow-up, the HZ incidence rate was 20.2 per 1,000 person-years (PY) in the HZ/su group and 70.9 per 1,000 PY in the placebo group. In the post hoc analysis, the VE in subjects with hematologic malignancies was 87.2% (95% CI: 44.2%, 98.6%) after a median follow-up time of 11 months.

Reactogenicity was common in this IC population. IS pain was the most commonly reported solicited local symptom, and fatigue, myalgia, and headache were the most commonly reported solicited general symptom following HZ/su administration. Any grade of fever was reported commonly (24.5%), but temperatures above 39.0°C were reported uncommonly (1.1%) in the HZ/su group. In general, the proportions of subjects reporting unsolicited AEs, SAEs, deaths, and pIMDs during the time periods assessed were similar between groups. Disease relapse or progression was reported in similar proportions in both groups. Numerical imbalances were noted in AEs of febrile neutropenia and SAEs of pneumonia, both observed mostly two weeks or more after vaccination. The clinical significance of the imbalances is unclear in this population, a majority of whom were receiving chemotherapy and were at higher baseline risk of these adverse events.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Prevention of HZ: Due to the heterogeneity of the patient populations, underlying diseases, and treatment profiles in the trials conducted in IC individuals, and the dominant study size of Zoster-002, the Applicant did not pool efficacy data across the IC studies. Presented below are select immunogenicity endpoints for the IC trials for the purposes of assessing immune responses to HZ/su in the IC populations and sub-populations evaluated. As these endpoints may have been primary, secondary, or exploratory depending on the trial, they are presented under section 7.1.6 ‘Other endpoints.’

Reviewer comment: *No agreed upon correlate of protection exists. Therefore, conclusions regarding efficacy cannot be determined from immunogenicity data.*

7.1.1 Methods of Integration

Data were not integrated.

7.1.2 Demographics and Baseline Characteristics

Please see reviews of the individual studies in sections 6.1.10.1, 6.2.10.1, and 9.2.

7.1.3 Subject Disposition

Please see reviews of the individual studies in sections 6.1.10.1, 6.2.10.1, and 9.2.

7.1.4 Analysis of Primary Endpoint(s)

VE was not integrated. Please see the presentation of VE in the individual trials in section 6.1.11 and 6.2.11.5.

7.1.5 Analysis of Secondary Endpoint(s)

Not applicable.

7.1.6 Other Endpoints

Humoral Immunogenicity:
The table below shows the anti-gE Ab VRR, GMC, and MGI for five of the trials that evaluated HZ/su in an IC population. Zoster-001 is not shown as the autoHCT population was also evaluated in Zoster-002, a larger study.

Table 58. VRR, GMC and MGI of anti-gE antibody ELISA concentrations in the HZ/su group pre-vaccination (Month 0) and at Months 2, 13 and 25 (ATP cohort for humoral immunogenicity)

Study	Population	Timepoint	VRR N	VRR n	VRR %	VRR LB 95% CI	VRR UB 95% CI	GMC N'	GMC value	GMC LB 95% CI	GMC UB 95% CI	MGI N	MGI Ratio	MGI value	MGI LB 95% CI	MGI UB 95% CI
Zoster-002	Overall	Pre	-	-	-	-	-	82	762.8	568.6	1023.5	-	-	-	-	-
		Month 2	82	55	67.1	55.8	77.1	82	12753.2	7973.0	20399.4	82	PII(M2)/ PRE	16.72	10.01	27.92
		Month 13	52	21	40.4	27.0	54.9	54	3183.8	1869.8	5421.2	52	PII(M13)/ PRE	4.51	2.58	7.89
		Month 25	38	17	44.7	28.6	61.7	39	2819.0	1387.1	5729.1	38	PII(M25)/ PRE	4.35	1.89	9.99
Zoster-028	Overall	Pre	-	-	-	-	-	87	1049.8	865.8	1273.0	-	-	-	-	-
		Month 2	87	75	86.2	77.1	92.7	87	18291.7	14432.1	23183.5	87	PII(M2)/ PRE	17.4	13.2	23.0
		Month 13	68	35	51.5	39.0	63.8	68	4477.3	3482.4	5756.3	68	PII(M13)/ PRE	4.3	3.4	5.6
	PreChemo	Pre	-	-	-	-	-	65	1032.3	821.0	1298.0	-	-	-	-	-
		Month 2	65	61	93.8	85.0	98.3	65	22974.3	19080.0	27663.5	65	PII(M2)/ PRE	22.3	17.1	29.0
		Month 13	51	27	52.9	38.5	67.1	51	4563.0	3532.8	5893.7	51	PII(M13)/ PRE	4.6	3.5	6.1
	OnChemo	Pre	-	-	-	-	-	22	1103.4	753.4	1616.0	-	-	-	-	-
		Month 2	22	14	63.6	40.7	82.8	22	9328.0	4492.5	19368.2	22	PII(M2)/ PRE	8.5	4.1	17.5
		Month 13	17	8	47.1	23.0	72.2	17	4229.5	2073.8	8626.0	17	PII(M13)/ PRE	3.6	2.0	6.4
Zoster-039	Overall	Pre	-	-	-	-	-	217	964.0	814.5	1140.8	-	-	-	-	-
		Month 2	217	142	65.4	58.7	71.7	217	13445.6	10158.9	17795.6	217	PII(M2)/ PRE	13.95	10.39	18.73
		Month 13	165	86	52.1	44.2	59.9	167	5202.7	4074.8	6642.8	165	PII(M13)/ PRE	4.97	3.73	6.61
	Excluding NHBCL and CLL	Pre	-	-	-	-	-	148	913.8	736.9	1133.2	-	-	-	-	-
		Month 2	148	119	80.4	73.1	86.5	148	24450.7	17991.9	33228.1	148	PII(M2)/ PRE	26.76	19.07	37.55
		Month 13	111	74	66.7	57.1	75.3	113	7127.9	5361.2	9476.7	111	PII(M13)/ PRE	7.57	5.33	10.76

Study	Population	Timepoint	VRR N	VRR n	VRR %	VRR LB 95% CI	VRR UB 95% CI	GMC N'	GMC value	GMC LB 95% CI	GMC UB 95% CI	MGI N	MGI Ratio	MGI value	MGI LB 95% CI	MGI UB 95% CI
Zoster-039 (cont'd)	CLL	Pre	-	-	-	-	-	36	928.6	614.0	1404.3	-	-	-	-	-
		Month 2	36	8	22.2	10.1	39.2	36	2620.7	1287.9	5332.9	36	PII(M2)/ PRE	2.82	1.50	5.30
		Month 13	25	5	20.0	6.8	40.7	25	2234.2	1210.5	4123.6	25	PII(M13)/ PRE	1.84	0.94	3.61
	NHBCL	Pre	-	-	-	-	-	33	1275.8	908.5	1791.5	-	-	-	-	-
		Month 2	33	15	45.5	28.1	63.6	33	5476.9	2985.7	10046.8	33	PII(M2)/ PRE	4.29	2.40	7.69
		Month 13	29	7	24.1	10.3	43.5	29	3161.7	1703.9	5866.7	29	PII(M13)/ PRE	2.32	1.34	4.01
Zoster-041	Overall	Pre	-	-	-	-	-	121	1354.4	1118.3	1640.4	-	-	-	-	-
		Month 2	121	97	80.2	71.9	86.9	121	19163.8	15041.5	24416.0	121	PII(M2)/ PRE	14.1	11.0	18.1
		Month 13	111	74	66.7	57.1	75.3	111	8545.1	6753.7	10811.5	111	PII(M13)/ PRE	6.4	5.1	8.0
Zoster-015	Overall	Pre	-	-	-	-	-	53	1218.4	895.0	1658.7	-	-	-	-	-
		Month 3	53	52	98.1	89.9	100	54	50443.0	40899.6	62213.2	53	PII(M3)/ PRE	41.15	29.65	57.13

Source: 125614/398.11, Response to IR dated June 7, 2021, Question 2, Table 1, pp. 3 - 5
Note: In February 2014, the assay cut-off was changed, following additional validation experiments, from 18 mIU/mL (used in Zoster-015) to 97 mIU/mL (used in the Zoster-002, Zoster-028, Zoster-039 and Zoster-041 studies)
VRR = vaccine response rate; GMC = geometric mean concentration; MGI = mean geometric increase; ATP = according to protocol; N = Number of subjects with pre- and post-vaccination results available (for VRR and MGI); N'= Number of subjects with available results (for GMC); n/% = Number / percentage of subjects with a vaccine response; 95% CI = 95% confidence interval; LB = Lower Bound; UB; Upper Bound; CLL = chronic lymphocytic lymphoma; NHBCL = non-Hodgkin B cell lymphoma
Excluding NHBCL and CLL = Multiple Myeloma, non-Hodgkin T-cell Lymphoma, Hodgkin Lymphoma and other hematologic malignancies
Vaccine response defined as:
For initially seronegative subjects, antibody concentration at post-vaccination ≥4 fold the cut-off for Anti-gE (4x97 mIU/mL)
For initially seropositive subjects, antibody concentration at post-vaccination ≥4 fold the pre-vaccination antibody concentration
Pre = Pre-vaccination (Month 0) (VRR and MGI are not applicable at the Pre timepoint)
Month 2 = one month post-dose 2
Month 13 = one year post-dose 2
Month 25 = two years post-dose 2
Month 3 = one month post-dose 2 in Zoster-015

Reviewer comment: *Anti-gE Abs in HZ/su recipients were statistically significantly increased over pre-vaccination levels for most of the trial populations shown above. A poor anti-gE Ab response was seen in subjects with CLL and NHBCL receiving or recently completed cancer therapy enrolled in Zoster-039.*

Cell-mediated immunity:
The table below shows the gE-specific CD4 T-cell frequencies.

Table 59. VRR and adjusted geometric mean of gE-specific CD4[2+] T-cells in the HZ/su group at Months 2, 13 and 25 (ATP cohort for cell-mediated immunogenicity)

Study	Population	Timing	VRR N	VRR n	VRR %	VRR LB 95% CI	VRR UB 95% CI	AGM N'	AGM Value	AGM LB 95% CI	AGM LB 95% CI
Zoster-002	Overall	Month 2	42	39	92.9	80.5	98.5	42	5397.0	4013.7	7231.8
		Month 13	27	19	70.4	49.8	86.2	27	1905.9	1352.0	2650.0
		Month 25	24	17	70.8	48.9	87.4	24	2265.5	1450.0	3466.2
Zoster-028	PreChemo	Month 2	22	11	50.0	28.2	71.8	22	781.8	535.2	1110.4
		Month 13	17	3	17.6	3.8	43.4	17	365.6	219.7	561.0
Zoster-039	Overall	Month 2	43	36	83.7	69.3	93.2	43	3054.3	2203.5	4196.8
		Month 13	33	22	66.7	48.2	82.0	34	1181.3	834.3	1636.4
	Excluding NHBCL and CLL	Month 2	19	14	73.7	48.8	90.9	19	2375.1	1549.3	3574.0
		Month 13	13	7	53.8	25.1	80.8	13	1106.0	671.9	1731.2
	CLL	Month 2	7	5	71.4	29.0	96.3	7	3922.2	1022.6	13283.6
		Month 13	2	2	100	15.8	100	2[#]	-	-	-
	NHBCL	Month 2	17	17	100	80.5	100	17	3706.0	2235.4	6036.9
		Month 13	18	13	72.2	46.5	90.3	18	1329.6	832.7	2049.7
Zoster-041	Overall	Month 2	28	20	71.4	51.3	86.8	28	1440.5	1044.4	1959.6
		Month 13	30	17	56.7	37.4	74.5	30	769.4	560.4	1033.4
Zoster-015*	Overall	Month 3	28	24	85.7	67.3	96.0	28	3375.63	2437.04	4632.87

Source: 125614/398.11, Response to IR dated June 7, 2021, Question 2, Table 2, p. 6
VRR = Vaccine response rate; ATP = according to protocol; AGM = adjusted geometric mean; N = Number of subjects with pre- and post-vaccination results available (for VRR); n/% = Number / percentage of subjects with a vaccine response; N'= number of subjects in a given category with available results (for adjusted GM); 95% CI = 95% confidence interval; LB = Lower Bound; UB; Upper Bound; CLL = chronic lymphocytic lymphoma; NHBCL = non-Hodgkin B cell lymphoma; Excluding NHBCL and CLL = Multiple Myeloma, non-Hodgkin T-cell lymphoma, Hodgkin lymphoma and other hematologic malignancies
*Vaccine response following induction with gE in all subjects for Zoster-015 is presented
[#]for CLL subgroup, only 2 subjects are included in HZ group therefore the adjusted geometric mean was not calculated since the model could not converge
Vaccine response defined as:
For initially subjects with pre-vaccination T-cell frequencies below the threshold, at least a 2-fold increase as compared to the threshold (2 x <320>Events/10E6 CD4+ T-cells)
For initially subjects with pre-vaccination T-cell frequencies above the threshold, at least a 2-fold increase as compared to pre-vaccination T-cell frequencies
Pre = Pre-vaccination (Month 0) (VRR and MGI are not applicable at the Pre timepoint)
Month 2 = one month post-dose 2
Month 13 = one year post-dose 2
Month 25 = two years post-dose 2
Month 3 = one month post-dose 2 in Zoster-015

Reviewer comment: *CMI assessments from each study may not be generalizable to the entire study populations due to the small size of, non-randomization of subjects to, and/or exclusion of certain study sub-populations from (for example, on chemo group in -028) the CMI analysis population.*

7.1.7 Subpopulations

See above for immunogenicity by underlying IC disease populations.

7.1.8 Persistence of Efficacy

Immunogenicity results were presented through 25 months post-vaccination in Zoster-002 above.

7.1.9 Product-Product Interactions

In general, the variety of immunosuppressive regimens used did not allow for analyses of immunogenicity by types of immunosuppressive medications.

7.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7.1.11 Efficacy Conclusions

There is no agreed-upon correlate of vaccine mediated protection against HZ; therefore, one cannot infer protection against HZ solely from post-vaccination immunogenicity responses generated in the supportive studies (Zoster-041, Zoster-028, Zoster-015, and Zoster-001). However, when data from these studies are evaluated in the context of the results generated from Zoster-002 and Zoster-039 (including vaccine efficacy data), they support a conclusion of effectiveness of HZ/su and the overall favorable risk/benefit of the use of HZ/su in diverse IC populations.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The Summary of Clinical Safety and Integrated Summary of Safety (ISS) included results from a pooled analysis of six clinical studies delineated in section 8.2.1 below. Reviews of these individual studies are located in sections 6.1 and 6.2, for the studies evaluating efficacy, and section 9.2 for the studies that did not evaluate efficacy.

These six studies evaluated HZ/su in five distinct IC populations. Despite the heterogeneity of these populations, integration of the safety data from these populations was performed to increase the likelihood of identifying potential rare events related to vaccination that might not be evident from individual studies enrolling small numbers of subjects. It was also performed to evaluate safety in certain subgroups, specifically subjects 18 – 49 YOA for whom HZ/su is not currently approved for use. Pooling in these subgroups allows more power to evaluate safety and is considered supplementary to the safety analyses performed on the individual study populations.

This integrated analysis will focus on all SAEs, fatal SAEs, Unsolicited AEs, and pIMDs.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The six studies included in the pooled analyses of safety met the following criteria:

- Treatment groups received the final vaccine formulation of HZ/su 50 µg gE/AS01$_B$ by intramuscular (IM) route of administration;

- Randomized, observer-blind, placebo-controlled studies with similar safety and reactogenicity follow-up and data collection; and
- Duration of follow-up was at least one year following the last dose of study vaccine.

Two studies (Zoster-015 and Zoster-001) used a three-dose schedule. Subjects who received three doses were included in this pooled safety analysis of unsolicited adverse events even though a three-dose schedule is not being proposed as a new dosing regimen.

Please see the table in section 5.3, which shows the six studies in the IC population pooled for this analysis.

Of the 3,116 subjects included in this analysis, 59.2% were enrolled in Zoster-002 and 18.0% were enrolled in Zoster-039. The remainder of the subjects were enrolled in Zoster-001 (2.9%; 3.7% of the pooled HZ/su group and 2.0% of the pooled placebo group), Zoster-015 (3.9%; 4.7% of the pooled HZ/su group and 3.2% of the pooled placebo group), Zoster-028 (7.4%), and Zoster-041 (8.5%).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Overall, in the pooled dataset from the six clinical trials in IC adults ≥18 YOA, 1,587 subjects received at least one dose of HZ/su and 1,529 received at least one dose of placebo.

Exposure

The table below shows the distribution of subjects that received exactly 1, 2, and 3 doses of HZ/su or placebo in the pooled dataset.

Table 60. Summary of vaccine exposure, ISS (TVC)

Total Number of Doses Received	HZ/su N=1587 n (%)	Placebo N=1529 n (%)
1	105 (6.6)	96 (6.3)
2	1397 (88.0)	1367 (89.4)
3	85 (5.4)	66 (4.3)
Any	1587 (100)	1529 (100)

Source: Adapted from 125614/398.0, ISS, Table 7, p. 93
ISS = integrated summary of safety; TVC = total vaccinated cohort; N = number of subjects in each group included in the considered cohort; n/% = number / percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least 1 dose

In the TVC in the pooled analysis, 93.3% of subjects randomized to receive HZ/su received at least two doses. A similar percentage of the placebo group (93.7%) received two doses.

Demographics

The table below shows the demographic composition of the pooled analysis.

Table 61. Summary of demographic characteristics, ISS (TVC)

Characteristic	HZ/su N=1587 n (%)	Placebo N=1529 n (%)	Total N=3116 n (%)
Age (years) at dose 1			
Mean SD	54.8 (12.54)	55.3 (12.45)	55.0 (12.5)
Median (min, max)	57.0 (18.0, 85.0)	57.0 (18.0, 87.0)	57.0 (18.0, 87.0)
Age Groups			

Characteristic	HZ/su N=1587 n (%)	Placebo N=1529 n (%)	Total N=3116 n (%)
18 – 49 years of age	443 (27.9)	419 (27.4)	862 (27.7)
≥50 years of age	1144 (72.1)	1110 (72.6)	2254 (72.3)
Gender			
Female	590 (37.2)	583 (38.1)	1173 (37.6)
Male	997 (62.8)	946 (61.9)	1943 (62.4)
Ethnicity			
American Hispanic or Latino	63 (4.0)	65 (4.3)	128 (4.2)
Not American Hispanic or Latino	1504 (96.0)	1445 (95.7)	2949 (95.8)
Missing	20 (-)	19 (-)	39 (-)
Geographic Ancestry/Race			
African Heritage / African American	30 (1.9)	32 (2.1)	62 (2.0)
American Indian or Alaskan Native	4 (0.3)	1 (0.1)	5 (0.2)
Asian - Central/South Asian Heritage	12 (0.8)	14 (0.9)	26 (0.8)
Asian - East Asian Heritage	171 (10.9)	190 (12.6)	361 (11.7)
Asian - Japanese Heritage	45 (2.9)	39 (2.6)	84 (2.7)
Asian - South East Asian Heritage	32 (2.0)	22 (1.5)	54 (1.8)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White - Arabic / North African Heritage	13 (0.8)	15 (1.0)	28 (0.9)
White - Caucasian / European Heritage	1211 (77.3)	1147 (76.0)	2358 (76.6)
Other	49 (3.1)	50 (3.3)	99 (3.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Missing	20 (-)	19 (-)	39 (-)

Source: Adapted from 125614/398.0, ISS, Table 8, p. 96
ISS = integrated summary of safety; TVC = total vaccinated cohort; N = total number of subjects in each group; n/% = number / percentage of subjects with a given characteristic; SD = Standard Deviation

Across both vaccine groups, vaccinated IC subjects had a mean (SD) age of 55.0 (12.5) years. Subjects were majority male (62.4%), white – Caucasian/European (76.6%), and not American Hispanic or Latino (95.8%). Demographic characteristics were also similar between vaccination groups within the two age strata (18 – 49 and ≥50 YOA).

8.2.3 Categorization of Adverse Events

For this pooled safety analyses, the most recent MedDRA version 22.1 was used, while in the analysis of individual studies previous MedDRA versions were used.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Pooling of the safety data from the six studies in the IC population is supported by use of the final formulation and similar safety assessment methods and duration of safety follow-up. The following safety monitoring was similar across studies:

- Solicited local and general AEs for seven days following each vaccination
- Unsolicited AEs and MAAEs for 30 days following vaccination
- SAEs from the first administered dose through 365 days following the last vaccination
- pIMDs from the first administered dose through 365 days following the last vaccination

Reviewer comment: *The method of collecting pIMDs has evolved over time. In studies Zoster-001 and -015, new onset autoimmune diseases and other immune-mediated inflammatory disorders were specified to be reported by the investigator through the study end. A pre-defined list of pIMDs was provided to the investigators in the protocol for the other four trials. After the completion of all studies included in this submission, GSK's pre-defined list of pIMDs was updated with the inclusion of 'gout' as an immune-mediated inflammatory process of interest. Gout is included as a pIMD below but was identified as such after study completion. pIMDs were collected in all studies, but as collection methods evolved, more PTs may have been identified as pIMDs in later studies. In particular, non-serious events of gout occurring beyond the assessment period for unsolicited AEs may not be reported in the studies.*

Zoster-002 study conclusion was based on accrual of HZ cases; therefore, safety follow-up included fatal SAEs, SAEs related to vaccination, pregnancies, and AEs of relapse or progression were collected through the end of the study, potentially beyond the 365 days following the last vaccination for some subjects. The safety follow-up period in other studies was one year post-vaccination.

Studies Zoster-015 and -001 included at least one arm with three doses of HZ/su. The pooled safety information on unsolicited AEs presented below includes AEs occurring after a third dose of HZ/su.

Reviewer comment: *Each of these five IC populations represents a distinct population with different profiles of disease risk. Zoster-002 is the largest study among the IC studies, representing 58.1% of the TVC who received HZ/su. Safety findings in this study dominate the pooled safety results.*

8.4 Safety Results

8.4.1 Deaths

The number and proportion of subjects in the integrated TVC who died during select time periods are shown in the table below.

Table 62. Summary of the incidence of deaths during the selected study periods, ISS (TVC)

Adverse Event	HZ/su N=1587 n (%)	Placebo N=1529 n (%)
First administered dose through 30 days post-last vaccination		
Deaths	2 (0.1)	7 (0.5)
Related deaths	- (-)	- (-)
First administered dose up to 365 days post-last vaccination		
Deaths	93 (5.9)	96 (6.3)
Related deaths	1 (0.1)	0 (0.0)
First administered dose up to study end		
Deaths	165 (10.4)	176 (11.5)
Related deaths	1 (0.1)	0 (0.0)

Source: Adapted from 125614/398.0, ISS Table 35, p. 161
ISS = integrated summary of safety; TVC = total vaccinated cohort; N = number of subjects included in the considered cohort in each group; n/% = number / percentage of subjects reporting at least one adverse event with a fatal outcome
"-" represents no event was reported across the treatment groups.

From the first vaccination through 30 days following the last vaccination, 2 subjects in the HZ/su group (0.1%) and 7 subjects in the placebo group (0.5%) died. From the first vaccination

through 365 days following the last vaccination, 93 subjects in the HZ/su group (5.9%) and 96 subjects in the placebo group (6.3%) died. In the 18 – 49 YOA group, no subjects died within 30 days of vaccination and 17 subjects (3.8%) in the HZ/su group and 19 subjects (4.5%) in the placebo group died within 365 days following the last vaccination.

Reviewer comment: *The proportion of subjects who died in the TVC of the pooled analysis during the time points evaluated were similar between treatment groups overall and by age strata.*

The two subjects who received HZ/su and died prior to 30 days after the last vaccination had fatal SAEs with PTs Cardiac failure (n=1) and Sepsis (n=1). Please see section 6.1.12.3 for a description of the fatal Cardiac failure. The subject who died of sepsis was a 64 YO woman with cervical cancer enrolled in Zoster-028 (who was receiving chemotherapy), who died of sepsis 4 days post-dose 2. No other information was provided regarding her death. In the placebo group through 30 days post-vaccination, no subjects died of a cardiac cause and one subject enrolled in Zoster-002 died of sepsis.

Reviewer comment: *There were few events of death reported from the first vaccination through 30 days following the last vaccination. Although specific causes for the deaths in the HZ/su group were not identified by the investigators (i.e., the cause of the cardiac failure, the causative organism of the sepsis), the events were singular, not atypical for the study population and more deaths were reported in the placebo group.*

From first vaccination through 365 days following the last vaccination, 93 subjects in the HZ/su group (5.9%) and 96 subjects in the placebo group (6.3%) in the pooled TVC died. The most commonly reported fatal SAEs by SOC during this time period, were reported by similar proportions of subjects in each treatment group and were in the SOC of Neoplasms benign, malignant and unspecified and the SOC of Infections and infestations. The most commonly reported fatal SAEs reported during this time period by PT were plasma cell myeloma (20 subjects, 1.3% in the HZ/su and 18 subjects, 1.2% in the placebo groups), sepsis (6 subjects, 0.4% in the HZ/su and 9 subjects, 0.6% in the placebo groups), and diffuse large B-cell lymphoma (6 subjects, 0.4% in the HZ/su and 3 subjects, 0.2% in the placebo groups) in the HZ/su group and plasma cell myeloma, sepsis, and pneumonia (5 subjects, 0.3% in the HZ/su and 9 subjects, 0.6% in the placebo groups) in the placebo group.

One fatal event of meningitis (verbatim term = “purulent meningitis”) was reported in an HZ/su recipient enrolled in Zoster-041. The event began within 17 days following dose 2 and “pulmonary sepsis” was also described in the narrative (see section 9.2.1). A reviewer-conducted analysis of all events with a PT containing “meningitis” revealed 8 events, 6 in the HZ/su group (including the above listed event) and 2 in the placebo group. Of the 8 events, no other events were fatal and 6 were reported more than 100 days after the most recent vaccination. The other event of meningitis occurring close to vaccination had a verbatim term of “subacute meningitis” and was reported 39 days following dose 2 of HZ/su in a subject enrolled in Zoster-039. This event occurred in the setting of a recurrence of the subject’s blastic plasmacytoid dendritic cell neoplasia and appeared from the narrative to be attributable to the cancer.

Reviewer comment: *A small imbalance in SAEs of meningitis was observed, though events do not cluster temporally close to vaccination.*

Comparative analyses, conducted by CBER, of deaths within 365 days following the last vaccination identified a numerical imbalance in fatal SAEs in the Hepatic disorders SMQ (6 subjects in the HZ/su and 1 subject in the placebo groups). Notably, 3 subjects in the HZ/su group and 0 in the placebo group had fatal SAEs of hepatitis B, which were also associated with other hepatic SAEs (Hepatitis fulminant, hepatic encephalopathy, and acute hepatic failure). Two of these events occurred in Zoster-039 in subjects receiving chemotherapy regimens potentially associated with hepatitis B reactivation, though only one of these subjects was clearly reported to have chronic hepatitis B (see section 6.2.12.3). The third fatal event of hepatitis B was reported 287 days following dose 2 of HZ/su in a subject enrolled in Zoster-002 whose MM had relapsed prior to the hepatitis B onset. Other fatal SAEs in the SMQ *Hepatic disorders* were Hepatic failure, Acute hepatic failure, and hepatic encephalopathy in the HZ/su group and Transaminases increased in the placebo group. Each of these fatal events in the SMQ *Hepatic disorders* had multiple complicating factors including progression of the underlying disease, sepsis, graft versus host disease of the liver, and potentially hepatotoxic and immunosuppressive medications. None of the fatal hepatic SAEs were assessed as related by investigators.

Reviewer comment: *Three fatal SAEs of Hepatitis B were reported in the HZ/su group. At least one of the subjects was known to have chronic hepatitis B and was not receiving antiviral prophylaxis. All of the subjects with hepatitis B were receiving or had recently received immunosuppressive medications. There were no additional (nonfatal) SAEs of hepatitis B reported in the ISS. All subjects with Hepatitis B and fatal hepatic events had other factors that could explain their liver pathology.*

For a discussion of deaths occurring after 365 days following the last vaccination, please see section 6.1.12.3, as Zoster-002 was the only trial that specified collection of events during this timeframe.

Related deaths: There was one fatal SAE of neonatal death in a neonate born to a woman who received HZ/su that was assessed by the investigator as related to vaccination (see section 9.1.1).

Fatal SAEs by age and region: None of the deaths reported up to 30 days following the last vaccination were reported in the 18 – 49 YOA group. Among HZ/su or placebo recipients, the percentage of subjects who died from first vaccination up to 365 days post-last vaccination was higher in the ≥50 YOA stratum compared to the 18 – 49 YOA stratum, as expected. Deaths reported through 30 and 365 days following the last vaccination were reported at similar frequencies between vaccination groups in the 18 – 49 and ≥50 YOA groups. No clinically significant differences in fatal SAEs were identified between vaccination groups in either age stratum.

There were no clinically significant differences between vaccination groups in deaths by region (North America and Other) up to 30 days and 365 day following last vaccination.

8.4.2 Nonfatal Serious Adverse Events

The Applicant's SAE analysis was performed on all SAEs, including fatal SAEs. The numbers and proportions of subjects reporting at least one SAE overall during specified time periods are below.

Table 63. Number and percentage of subjects reporting at least one SAE during select time periods, ISS (TVC)

Adverse Event	HZ/su N=1587 n (%)	Placebo N=1529 n (%)
First vaccination up to 30 days post-last vaccination		
All SAEs	114 (7.2)	118 (7.7)
Related SAEs	1 (0.1)	3 (0.2)
First vaccination up to 365 days post-last vaccination		
All SAEs	410 (25.8)	405 (26.5)
Related SAEs	5 (0.3)	6 (0.4)

Source: Adapted from 125614/398.0, ISS, Table 30, p. 150
SAE = serious adverse event; ISS = integrated summary of safety; TVC = total vaccinated cohort; N = number of subjects included in each group; n/% = number / percentage of subjects reporting the adverse event at least once

Reviewer comment: *Overall, the proportion of subjects reporting SAEs up to 30 days following the last vaccination is balanced between vaccination groups. A reviewer generated analysis excluding SAEs related to HZ did not appreciably alter the proportions presented above.*

From the first dose up to 30 days after the last dose, 7.2% of subjects who received HZ/su and 7.7% of subjects who received placebo in the pooled analysis reported SAEs. By SOC, the most frequently reported SAEs in the HZ/su and placebo groups were Infections and infestations (46 subjects, 2.9% and 38 subjects, 2.5%, respectively), Neoplasms benign, malignant and unspecified (1.8% and 2.6%, respectively) and Blood and lymphatic system disorders (1.2% and 1.0%, respectively). By PT, the most frequently reported SAEs in the HZ/su and placebo groups were Pneumonia (17 subjects, 1.1% and 7 subjects 0.5%, respectively), Febrile neutropenia (15 subjects, 1.0% and 7 subjects, 0.5%), and Plasma cell myeloma (8 subjects, 0.5% and 13 subjects, 0.9%).

A numerical imbalance between the HZ/su and placebo groups is noted in SAEs reported from first vaccination up to 30 days following the last vaccination in the PT of Pneumonia (see above), as well as the HLT of Lower respiratory tract and lung infections (20 subjects, 1.3% and 8 subjects, 0.5%) and the SMQ *Infective pneumonia* (21 subjects, 1.3% and 11 subjects, 0.7%, respectively). Non-serious AEs during the 30-day post-vaccination period with a PT in the SMQ *Infective pneumonia* were not imbalanced. All SAEs during this time period in the SMQ *Infective PNA* were reported in Zoster-002 and Zoster-039. The onset day ranged from the day of (second) vaccination to 53 days following vaccination in the HZ/su group and from 5 to 39 days following vaccination in the placebo group. Onset in the HZ/su group was distributed throughout this range, though a majority of events in Zoster-002 were reported in the first two weeks post-vaccination and a majority in Zoster-039 were reported more than two weeks post-vaccination. None of the SAEs of Infective pneumonia up to 30 days post-last vaccination were assessed as related by investigators. In addition, 3 subjects in the HZ/su group and no subjects in the placebo group reported SAEs in the SMQ *Interstitial lung disease* (PTs of Pneumonitis, n=2, and Interstitial lung disease). One subject enrolled in Zoster-001, per the narrative was diagnosed with pneumonitis due to radiotherapy or chemotherapy vs. community acquired pneumonia 41 days after dose 2. The other event with a PT of Pneumonitis, occurred in Zoster-002 8 days following dose 1 of HZ/su and was described as a “superinfection at the lung bases” per chest computed tomography. The last event was an Interstitial lung disease (drug-induced pneumonitis) pIMD beginning on the day of dose 2 (see section 8.4.8 for details).

Reviewer comment: *There is a numerical imbalance in SAEs of* Infective pneumonia *between the HZ/su and placebo groups that was observed in two studies, Zoster-002 and -039. Two*

additional SAEs of pneumonitis may also represent pulmonary infectious processes. In the pooled analysis, the greatest imbalance is observed in the first two weeks following any vaccination; although this is dominated by Zoster-002 and a similar pattern in onset day was not see in Zoster-039. There are biologically plausible mechanisms by which HZ/su could contribute to an imbalance in pneumonia. SAEs in the SOC Infections and infestations were balanced between groups at the 30-day post-vaccination time point in the ISS (2.9% in the HZ/su and 2.5% in the placebo groups). At two weeks post-vaccination, an imbalance in SAEs in the SOC Infections and infestations is attributable to pneumonia. However, imbalances were also noted in unsolicited AEs in ear infections (see section 8.4.4). Arguing against this imbalance being clinically significant, a similar proportion of subjects died of pneumonia in the HZ/su group and the placebo group up to 30 days following the last vaccination (0 subjects and 2 subjects, 0.1%) and 365 days following the last vaccination (7 subjects, 0.4% and 11 subjects, 0.7%, respectively). In summary, this imbalance was observed in two studies and a causal link to vaccination is possible.

A numerical imbalance is also noted in the pooled analysis between the HZ/su and placebo groups in SAEs reported up to 30 days following the last vaccination with PT of Febrile neutropenia (15 subjects, 1.0% and 7 subjects, 0.5%, respectively). Narrow SMQs containing this term were numerically imbalanced (HZ/su > placebo) during this time period, though to a lesser degree: *Agranulocytosis* (18 subjects, 1.1% and 10 subjects, 0.7%, respectively) and the sub-SMQ *Hematopoietic leukopenias* (18 subjects, 1.1% and 12 subjects, 0.8%, respectively). Other PTs in these SMQs were not imbalanced (Neutropenic sepsis, Agranulocytosis, Neutropenia, and Pancytopenia). No events of febrile neutropenia were assessed as related by investigators. The imbalance in Febrile neutropenia was identified primarily in Zoster-039 (7 subjects, 2.5% in the HZ/su and 2 subjects, 0.7% in the placebo groups) and Zoster-028 (4 subjects, 3.4% in the HZ/su and 2 subjects, 1.7% in the placebo groups). Febrile neutropenia was not notably imbalanced in studies enrolling subjects post-autoHCT (4 subjects in the HZ/su and 3 subjects in the placebo groups of Zoster-002 and -001). The Applicant notes that a majority of these subjects with SAEs of febrile neutropenia in -039 and all of the subjects in -028 had chemotherapy within 15 days prior to the onset of the SAE.

Reviewer comment: *There is a numerical imbalance in SAEs of Febrile neutropenia reported more frequently in the pooled analysis in the HZ/su group up to 30 days following the last vaccination. This imbalance was noted most prominently in Zoster-039, which enrolled subjects with hematologic malignancies, some receiving chemotherapy, and less so in Zoster-028, which enrolled subjects with solid tumors undergoing chemotherapy. This population is at risk of neutropenia and febrile neutropenia due to disease and anti-neoplastic therapies. Please see the discussion of the SAEs of febrile neutropenia in Zoster-039 in section 6.2.12.2 for the reviewer's assessment that these events are not likely to be caused by vaccination based on timing and distribution of related events, such as neutropenia. In the pooled analysis, unsolicited AEs in the sub-SMQ* Hematopoietic leukopenias *(which includes febrile neutropenia, as well as neutropenia), in the 30-day post-vaccination period was also balanced between the HZ/su and placebo groups (69 subjects, 4.4% and 60 subjects, 3.9%, respectively), suggesting the between-group difference is not due to a difference in neutropenia between groups. No SAEs of Febrile neutropenia in the HZ/su group were reported within the week after vaccination, suggesting that post-vaccination reactogenicity did not contribute to this imbalance.*

From the first dose up to 365 days after the last dose, 25.8% of subjects who received HZ/su and 26.5% of subjects who received placebo in the pooled analysis reported SAEs. By SOC, the most frequently reported SAEs in the HZ/su and placebo groups were Infections and infestations (11.9% and 11.3%, respectively), Neoplasms benign, malignant and unspecified

(10.6% and 10.3%, respectively) and Blood and lymphatic system disorders (3.2% and 2.9%, respectively). By PT, the most frequently reported SAEs in the HZ/su and placebo groups were Plasma cell myeloma (64 subjects, 4.0% and 48 subjects, 3.1%), Pneumonia (57 subjects, 3.6% and 48 subjects 3.1%, respectively), and Febrile neutropenia (31 subjects, 2.0% and 24 subjects, 1.6%).

Reviewer comment: *Overall, the proportion of subjects reporting SAEs up to 365 days following the last vaccination is balanced between vaccination groups. The most frequently reported PTs were also balanced, specifically pneumonia and febrile neutropenia, for which a numerical imbalance was observed at the 30-day time point. The Applicant also notes numerical imbalances in the PTs of Influenza (12 subjects, 0.8% in the HZ/su and 5 subjects, 0.3% in the placebo groups), Lower respiratory tract infection (8 subjects, 0.5% in the HZ/su and 4 subjects, 0.3% in the placebo groups), and Upper respiratory tract infection (7 subjects, 0.4% in the HZ/su and 2 subjects, 0.1% in the placebo groups). The HLT of lower respiratory tract infection, as well as the SMQ* Infective pneumonia *is balanced during this period. There does appear to be a small numerical imbalance in the low number of subjects that reported SAEs of Influenza and Upper respiratory tract infection over the one year following vaccination. Given the small size of these numerical imbalances in a small number of subjects reporting these events, they are not likely to represent clinically significant between-group differences.*

An imbalance was observed with more HZ/su subjects than placebo group subjects reporting SAEs up to 365 days following the last vaccination in the SOC Hepatobiliary disorders (13 subjects, 0.8% and 3 subjects, 0.2%, respectively). With regard to Hepatobiliary disorders, the PTs in the HZ/su group included Cholelithiasis, Acute hepatic failure, and Portal hypertension in two subjects each, and Bile duct stone, Bile duct obstruction, Cholecystitis chronic, Hepatitis cholestatic, Hepatic failure, Hepatitis fulminant, and Hepatitis toxic in one subject each. In the placebo group, the PTs included one subject with Cholecystitis and Cholelithiasis, and one subject each with Bile duct stone, and Hepatic function abnormal. A majority of the events occurred in Zoster-002 (9 subjects in the HZ/su and 3 subjects in the placebo groups), with an additional two subjects in the HZ/su group in Zoster-039 (both events involving hepatitis B infection, discussed above in section 8.4.1), one subject each in the HZ/su group in Zoster-015 (Portal hypertension) and Zoster-041 (Cholelithiasis) reporting such events. A greater difference between the HZ/su and the placebo groups was noted in the HLGT of Hepatic and hepatobiliary disorders (8 subjects, 0.5% and 1 subject, 0.1%, respectively) compared to Bile duct disorders (2 subjects and 1 subject, respectively) or Gallbladder disorders (3 subjects and 1 subject, respectively). One subject who reported an SAE of Portal hypertension had a prior history of cirrhosis. The other subject was enrolled into Zoster-015, had no history of liver disease, and reported Portal hypertension (verbatim term “non-cirrhotic portal hypertension”) with Esophageal varices hemorrhage 97 days post-dose 2, exact cause unknown but suspected by the investigator to be exposure to didanosine taken 12 years earlier. There is no indication in either narrative of portal vein thrombosis. The Applicant notes that none of the SAEs in the Hepatobiliary disorders SOC were assessed as related by investigators.

Reviewer comment: *There is an imbalance in the ISS in SAEs in the SOC Hepatobiliary disorders, and more specifically in the HLGT of Hepatic and hepatobiliary disorders. Relatively small numbers of subjects reported SAEs in this SOC. Please see the discussion of fatal SAEs in SOC Hepatobiliary disorders in section 8.4.1 above, which includes some events included here. The narratives for SAEs in this HLGT were reviewed and all subjects have other factors that likely contributed to their hepatic disease.*

The reviewer also noted an imbalance in the SOC Musculoskeletal disorders (16 subjects, 1.0% and 6 subjects, 0.4%, respectively). Relatively small numbers of subjects reported SAEs in the SOC. The PTs represented a variety of PTs. With the exception of the HLGT of Musculoskeletal and connective tissue deformities, which includes Intervertebral disc disorders (PTs of Intervertebral disc disorder and Intervertebral disc protrusion) and Spine and neck deformities (Kyphosis, Lumbar spinal stenosis, and Spondylolisthesis), reported by 5 subjects in the HZ/su group and 0 subjects in the placebo group, HLGTs were either reported in a single subject or were reported by a similar number subjects in both groups. The reviewer is not aware of a biologically plausible mechanism by which HZ/su would contribute to an imbalance in spine disorders.

The Applicant also discusses an imbalance in the PT of Hodgkin's lymphoma (12 subjects, 0.8% in the HZ/su and 3 subjects, 0.2% in the placebo groups). All but one of these subjects in the HZ/su group, reported an SAE of Hodgkin's disease that was a relapse of pre-existing disease. The Applicant notes that there were no between group differences in all events of disease relapses and disease progressions during the whole study period for Zoster-002, from which a majority of SAEs of Hodgkin's disease were reported.

Reviewer comment: *The imbalance in Hodgkin's disease appears to be artifact. SAEs in the SOC Neoplasms benign, malignant and unspecified, as well as the sub-SMQ Hematological malignant tumors were balanced between vaccine groups. In addition, the difference may represent a difference in classification of seriousness, which may vary based on hospitalization practices and investigator discretion of identifying an event as medically significant and thus, serious. Serious and non-serious events of relapse and progression were collected for the entire study period in Zoster-002. A reviewer analysis of all events (serious and non-serious) of Hodgkin's disease in the ISS up to 365 days following the last vaccination shows less of an imbalance between the HZ/su and placebo groups (17 subjects, 1.1% and 10 subjects, 0.7%, respectively). This is not likely to be clinically significant.*

The Applicant did not identify any SAEs reported more frequently in the placebo group compared to the HZ/su group (LB of the 95% CI of RR >1) up to 30-days post-last vaccination in their exploratory analysis.

Related SAEs: One subject in the HZ/su group (0.1%) and three subjects in the placebo group (0.2%) reported an SAE assessed as related up to 30 days following vaccination. In the HZ/su group, the subject was hospitalized for Neutropenia (verbatim term "exacerbation of neutropenia"), assessed as related, and pneumonia, assessed as unrelated, beginning day 13 after dose 1 (see section 6.1.12.4). This subject recovered after 15 days and did not receive a second dose. The PTs assessed by investigators as related in the placebo group were Constipation, HZ, and toxic skin eruption.

Up to 365 days following the last vaccination, five subjects (0.3%) in the HZ/su group reported seven SAEs assessed as related and six subjects (0.4%) in the placebo group reported eight SAEs assessed as related. No additional related SAEs were reported through the study end (pertinent for Zoster-002 only). The related SAEs from 30 days up to 365 days following the last vaccination in the HZ/su group are as follows:

- Pneumonia day 105 after dose 2 of HZ/su: A 57 YO woman who was post-autoHCT for multiple myeloma was hospitalized with an organizing pneumonia (PT of Pneumonia) which the investigator assessed as related because the subject had no prior history of a similar event, the SAE had a temporal relationship within 3 months of the last dose of vaccine, and the symptoms resolved without recurrence.

- Atrial fibrillation, cutaneous vasculitis, and arthralgia beginning 120 – 122 days after dose 2 (as two of three of these concurrent events were pIMDs, see section 8.4.8)
- Autoimmune thrombocytopenia 136 days after dose 2 (see section 8.4.8)
- Neonatal death following dose 2, see Pregnancy (see section 9.1.1)

The PTs of SAEs assessed by investigators as related occurring 30 or more days following vaccination in the placebo group were: Burkitt's lymphoma, Febrile neutropenia, and Mucosal inflammation in one subject and herpes zoster cutaneous disseminated and Guillain-Barre syndrome in one subject each.

Reviewer comment: *The reviewer agrees there was no identified cause for several of the events assessed by investigators as related to investigational product. However, the variety of types of events and the timing (most events occurred more than three months following vaccination) do not suggest a safety concern.*

SAEs by age: The incidence of SAEs up to 30 days following the last vaccination was similar between the HZ/su and placebo groups within each age stratum:18 – 49 YOA (28 subjects, 6.3% and 22 subjects, 5.3%, respectively) and ≥50 YOA (86 subjects, 7.5% and 96 subjects, 8.6%, respectively). Up to 365 days following the last vaccination, the incidence of SAEs was similar between the HZ/su and placebo groups within each age stratum:18 – 49 YOA (78 subjects, 17.6% and 88 subjects, 21.0%, respectively) and ≥50 YOA (332 subjects, 29.0% and 317 subjects, 28.6%, respectively).

The Applicant identified no clinically relevant imbalances by primary SOC or by individual PTs. The imbalances noted above in the entire pooled population were generally distributed throughout both age strata with the following exceptions:

- The imbalance in Hodgkin's disease was primarily in the 18 – 49 YOA stratum (9 subjects, 2.0% in the HZ/su and 2 subjects, 0.5% in the placebo groups reporting an SAE of Hodgkin's disease up to 365 days following the last vaccination). The SOC of Neoplasms benign, malignant, and unspecified was balanced in this age group. Please see the discussion above regarding Hodgkin's disease.
- The imbalance noted in the SOC Hepatobiliary disorders and SOC Musculoskeletal up to 365 days post-vaccination was primarily in the ≥50 YOA stratum. See the discussion above regarding these SOC imbalances.
- A reviewer-conducted analysis of SAEs by SOCs, PTs, and SMQs identified potentially clinically relevant differences between the HZ/su and placebo groups in the 18 – 49 YOA stratum in the SOC Infections and Infestations up to 30 days following the last vaccination (14 subjects, 3.2% and 7 subjects, 1.7%, respectively) and the SMQ *Infective pneumonia* up to 30 days following the last vaccination (6 subjects, 1.4% and 1 subject, 0.2%, respectively) and up to 365 days following the last vaccination (16 subjects, 3.6% and 6 subjects, 1.4%, respectively). In this age stratum, up to 365 days following the last vaccination, the proportions of subjects reporting SAEs in the SOC of Infections and infestations was similar between the HZ/su and placebo groups (39 subjects, 8.8% and 31 subjects, 7.4%, respectively). Up to 365 days following the last dose, in the HZ/su 18 – 49 YOA group, SAEs with a PT of pneumonia were reported more frequently than in the placebo group (11 subjects, 2.5% in the HZ/su and 6 subjects, 1.4% in the placebo groups), as well as SAEs with a PT in which the causative organism of the pneumonia was specified (6 subjects, in the HZ/su and 0 subjects in the placebo group). Organisms included unspecified, fungal, pseudomonas, pneumocystis jiroveci, respiratory syncytial virus, and aspergillus; in the placebo group, all organisms

were unspecified in the datasets. Onset was between 2 to 319 days following a dose of HZ/su and there was no clear clustering. A smaller numerical imbalance in SAEs with a PT in the SMQ of *Sepsis* was also seen up to 365 days post-last vaccination in the 18 – 49 YOA stratum (6 subjects, 1.4% in the HZ/su and 3 subjects, 0.7% in the placebo groups), with onset in the HZ/su group 19 – 277 days after vaccination, with no clustering of events in time.

Reviewer comment: *The imbalance in SAEs of pneumonia was more pronounced in the 18 – 49 YOA stratum compared to the ≥50 YOA stratum up to 30 days post-last vaccination. The imbalance was also observed in the younger age stratum at the 365 days post-last vaccination. In the older age stratum, SAEs of Infective pneumonia are similar in the HZ/su and placebo groups at the one-year time point (5.5% and 5.0%, respectively). In the 18 – 49 YOA stratum, fewer subjects were enrolled and fewer reported SAEs and the proportion of subjects reporting such SAEs was low overall.*

8.4.3 Study Dropouts/Discontinuations

There was a total of 571 (18.3%) withdrawals, 271 subjects (17.1%) in the HZ/su group and 300 subjects (19.6%) in the placebo group) before last study visit or Visit 5/M25 in Zoster-002. An SAE was the most common reason for withdrawal; it was the primary reason for 9.1% of subjects in the HZ/su and 10.1% of subjects in the placebo groups. The proportion of subjects with a non-serious AE as the reason for withdrawal was also balanced between the HZ/su and placebo groups (1.6% and 1.4%, respectively). The proportions of subjects with SAEs leading to withdrawal, while higher in the ≥50 YOA stratum (10.8% in HZ/su and 11.5% in the placebo group) compared to 18-49 YOA stratum (4.7% in the HZ/su group and 6.2% in the placebo group), were balanced between vaccination groups within age strata.

Nine AEs (6 in the HZ/su group and 3 in the placebo group) were assessed as related and led to treatment discontinuation or resulted in the subject not completing the dose 2 vaccination visit (please see the individual study sections for additional details):

- Neutropenia (HZ/su, serious, Zoster-002)
- Psoriasis (HZ/su, non-serious, Zoster-002)
- Myalgia (HZ/su, non-serious, Zoster-002)
- Neutropenia (HZ/su, non-serious, Zoster-002)
- Tachycardia (HZ/su, non-serious, Zoster-028)
- Fever (HZ/su, non-serious, Zoster-041)
- Toxic skin eruption (placebo, serious, Zoster-002)
- Discoid eczema (placebo, non-serious, Zoster-002)
- Constipation (placebo, serious, Zoster-002)

An additional two subjects in Zoster-015 did not receive dose 3 of HZ/su for AEs that were assess as related (a solicited, non-serious AE of fatigue and a non-serious, medically attended AE of ILI).

Reviewer comment: *The high rate of withdrawal (18.3%) is attributable to the following: the withdrawal rate in Zoster-002 through the M25 visit (as opposed to M13) is presented, the dominant size of Zoster-002, and the medical conditions of the study populations, particularly for the two largest studies. In the pooled analysis, withdrawals from treatment and from the study were similar between vaccination groups. Few events that were considered related to vaccination led to discontinuation from treatment or study.*

8.4.4 Common Adverse Events

Unsolicited AEs

The table below displays the number and proportions of subjects in the TVC of the pooled analysis who reported unsolicited AEs within the 30-day post-vaccination period.

Table 64. Summary of subjects reporting the occurrence of at least one unsolicited AE (serious and non-serious) of various types within the 30-day (Days 0-29) post-vaccination period, ISS (TVC)

Adverse Event	HZ/su N=1587 n (%)	Placebo N=1529 n (%)
All unsolicited AEs	733 (46.2)	675 (44.1)
Related unsolicited AE	87 (5.5)	47 (3.1)
Medically attended unsolicited AE	409 (25.8)	365 (23.9)
Related medically attended unsolicited AE	18 (1.1)	10 (0.7)

Source: Adapted from 125614/398.0, ISS Table 26, p. 125
AE = adverse event; ISS = integrated summary of safety; TVC = total vaccinated cohort; N = number of subjects with at least one administered dose; n/% = number / percentage of subjects reporting the symptom at least once

Reviewer comment: *In the pooled analysis, the incidence of unsolicited AEs, serious and non-serious, during the 30-day post-vaccination period was similar for the HZ/su and placebo groups; however, related unsolicited AEs (as per investigator assessment) were reported more frequently in the HZ/su group compared to the placebo group. A reviewer generated analysis excluding AEs related to HZ did not appreciably alter the proportions presented above.*

For all unsolicited AEs in the 30-day post-vaccination period, the most frequently reported SOCs in both the HZ/su and placebo groups were Infections and infestations (16.3% and 15.2%, respectively), Gastrointestinal disorders (11.1% and 10.2%, respectively) and General disorders and administration site conditions (11.0% and 9.0%, respectively). The most frequently reported events in both groups (>2% in the HZ/su group) by PT were Upper respiratory tract infection (48 subjects, 3.0% in the Hz/su and 35, 2.3% in the placebo groups), Nausea (47 subjects, 3.0% in the HZ./su and 43 subjects, 2.8% in the placebo groups), Nasopharyngitis (44 subjects, 2.8% in the HZ/su and 46 subjects, 3.0% in the placebo groups), Cough (44 subjects, 2.8% in the HZ/su and 31 subjects, 2.0% in the placebo groups), Neutropenia (43 subjects, 2.7% in the HZ/su and 47 subjects, 3.1% in the placebo groups), Diarrhea (41 subjects, 2.6% in the HZ/su and 30 subjects, 2.0% in the placebo groups), and Asthenia (38 subjects, 2.4% in the HZ/su and 42 subjects, 2.8% in the placebo groups).

Reviewer comment: *The most frequently reported unsolicited AEs were reported at relatively similar frequencies between treatment groups in the 30-day post-vaccination period.*

The Applicant has identified the following imbalances by the PT being reported in ≥1% of subjects in the HZ/su group and at a rate at least 1.5-fold higher than placebo group for which they considered inclusion in the PI:

- Arthralgia: Reported by 24 subjects (1.5%) in the HZ/su group and 15 subjects (1.0%) in the placebo group. In the HZ/su group, 6 of the events were considered related by the investigator; 15 events occurred within 7 days (Days 0-6) post-vaccination, 14 of which were co-reported with solicited local and general AEs. In the placebo group, 2 events were assessed as related by the investigator and 9 events occurred within 7 days post-vaccination. The Applicant proposes to include Arthralgia in section 6.1 of the US PI.

  Reviewer comment: *The reviewer agrees with inclusion in the US PI. Of note, the imbalance in arthralgia was primarily noted in North America when analyzed by region.*

- ILI: Reported by 21 subjects (1.3%) in the HZ/su group and 9 subjects (0.6%) in the placebo group. In the HZ/su group, 9 of the events, all of which occurred within 7 days post-vaccination, were assessed as related by the investigator; 13 events in total occurred within 7 days post-vaccination and were all co-reported with solicited local and general AEs. No events of cough or acute respiratory illness were co-reported as unsolicited AEs. In the placebo group, all 9 events were assessed as not related by the investigator and 3 of the 9 events occurred within 7 days post-vaccination.

  Reviewer comment: *Influenza is noted in the 30-day post-vaccination period in 6 subjects in the HZ/su group (0.4%) and 8 subjects in the placebo group (0.5%). Consequently, the ILI imbalance does not appear to suggest an imbalance in influenza. CBER recommended inclusion of this event in the PI, as events are potentially related to vaccination and were not uncommon.*

- Pneumonia: Reported by 19 subjects (1.2%) in the HZ/su group and 10 subjects (0.7%) in the placebo group. The Applicant reports the unsolicited AEs of pneumonia ranged between 0-29 days after vaccination in the HZ/su group. Five events (3 in HZ/su group and 2 in placebo group) occurred within 7 days of vaccination. All events in both vaccination groups were assessed as not related by the investigator. The Applicant does not consider this relevant for inclusion in the PI because there were no clinically relevant imbalances in the SOC of Infections and Infestations or other similar events (Narrow SMQ *Infective pneumonia*) per their assessment.

  Reviewer comment: *The SMQ Infective pneumonia is a better indicator of all cases of pneumonia. A similar imbalance was evident in unsolicited AEs in the SMQ Infective pneumonia within the 30-day post-vaccination period, with 24 (1.5%) of subjects in the HZ/su group and 14 subjects (0.9%) in the placebo group reporting such events. A majority of these events were SAEs; please see the discussion in section 8.4.2. CBER recommended inclusion of this event in the PI as it met the Applicant's stated criteria for inclusion, the imbalance suggests the events could potentially be related to vaccination, and the events were not uncommon.*

The Applicant identified the following imbalances that were statistically significant in their exploratory analyses, but which were reported in a low proportion of the population and which they do not consider clinically significant for inclusion in the PI:

- Injection site pruritis: 12 subjects (0.8%) in the HZ/su group and 1 subject (0.1%) in the placebo group. The Applicant notes that this unsolicited AE was included in the PI in section 6.1 for older adults.

- Eczema: 7 subjects (0.4%) in the HZ/su group and none in the placebo group. All the events were non-serious, were assessed as not related by the investigator and presented from 0-27 days after vaccination. The Applicant also notes these events may be confounded by concomitant medications.

  Reviewer comment: *In a CBER analysis unsolicited AEs with PTs in the HLT of Dermatitis and eczema were reported in 19 subjects in the HZ/su group (1.2%) and 4 subjects in the placebo group (0.3%). None of these events were serious or assessed by investigators as related. This imbalance was not noted in the original BLA in the older adult studies.*

- Ear infection: 6 subjects (0.4%) in the HZ/su group and none in the placebo group. All the events were non-serious, were assessed as not related by investigator, and began 2-29 days after vaccination, with no clustering closer to vaccination.

  Reviewer comment: *In a CBER analysis, unsolicited AEs with PTs in the HLT of Ear infections (including the PT otitis media) was reported in 8 subjects (0.5%) in the HZ/su group and no subjects in the placebo group, again with no clustering in time.*

- Edema: 5 subjects (0.3%) in the HZ/su group and none in the placebo group. All the reported events were non-serious, were assessed as not related by the investigators, and began from 0-17 days after vaccination. The Applicant notes that edema can be an element of multiple medical conditions. In addition, the HLT Edema is balanced between vaccination groups.

The Applicant also notes that the following PTs were reported statistically significantly more frequently in the placebo group in the 30-day post-vaccination period: Odynophagia, Hypomagnesemia, AML, and Hot flush.

Unsolicited AEs by age: In the 18 – 49 YOA stratum, the incidence of unsolicited AEs (serious and non-serious) within the 30-day post-vaccination period in the HZ/su and placebo groups was 44.9% and 39.1%, respectively. The most frequently reported SOCs in this age stratum in both the HZ/su and placebo groups were Infections and infestations (80 subjects, 18.1% and 56 subjects, 13.4%, respectively), Gastrointestinal disorders (56 subjects, 12.6% and 38 subjects, 9.1%, respectively), and General disorders and administration site conditions (49 subjects, 11.1% and 35 subjects, 8.4%, respectively). The most frequently reported PTs (reported in >3% of subjects) were Nausea (18 subjects, 4.1% in the HZ/su and 10 subjects, 2.4% of the placebo groups), Nasopharyngitis (17 subjects, 3.8% in the HZ/su and 12 subjects, 2.9% in the placebo group), Upper respiratory tract infection (15 subjects, 3.4% in the HZ/su and 9 subjects, 2.1% in the placebo group), Asthenia (15 subjects, 3.4% in the HZ/su and 5 subjects, 1.2% in the placebo groups), and Diarrhea (15 subjects, 3.4% in the HZ/su and 2 subjects, 0.5% in the placebo groups) in the HZ/su group. The only PT reported in more than 3% of subjects in the placebo group was Alopecia (8 subjects, 1.8% in the HZ/su and 13 subjects, 3.1% in the placebo groups). The Applicant identifies an imbalance in the PT of Diarrhea, which was higher in the HZ/su group compared to placebo group, as a clinically significant imbalance. Diarrhea is included in the solicited adverse reaction of GI symptoms in the PI.

Reviewer comment: *The most frequently reported SOCs in the 18 – 49 YOA stratum are numerically imbalanced between the vaccine groups. With the exception of the SAEs of Infective pneumonia, which are discussed with SAEs above, there were no clinically significant imbalances identified within the MedDRA hierarchy in the SOC Infections and infestations. Clinically relevant imbalanced PTs in the SOC Gastrointestinal disorders and General disorders and administration site conditions are noted above (for example, nausea, diarrhea, and asthenia) or are similar to imbalances noted elsewhere (for example, ILI).*

In addition, the reviewer noted imbalances in subjects 18 – 49 YOA between the HZ/su and placebo groups in the SOCs of Investigations (16 subjects, 3.6% and 2 subjects, 0.5%, respectively) and Respiratory, thoracic and mediastinal disorders (37 subjects, 8.4% and 19 subjects, 4.5%, respectively) as well as a small numerical imbalance in the SOC Cardiac disorders (5 subjects, 1.1% and no subjects, respectively). No clinically significant imbalances within the MedDRA hierarchy within these SOCs were identified. PTs in the SOC Cardiac

disorders in this age stratum were Palpitations (3 subjects in the HZ/su group), and one subject each in the HZ/su group with Cardiovascular disorder (Verbatim term "circulation problems" assessed as not related) and Tachycardia. Two of the three events of palpitations or tachycardia in close temporal association with vaccination were assessed as related. None of the Cardiac disorders AEs were serious.

CBER-conducted between-group comparisons of SMQs for subjects 18 – 49 years of age revealed numerical imbalances in Hematopoietic leukopenias (18 subjects, 4.1% in the HZ/su and 10 subjects, 2.4% in the placebo groups) and Infective pneumonia (see section 8.4.2). Only six of the unsolicited AEs in the sub-SMQ Hematopoietic leukopenias were serious (4 subjects in the HZ/su and 2 subjects in the placebo group). Unsolicited AEs (serious and non-serious) in the sub-SMQ Hematopoietic leukopenias in subjects ≥50 YOA were not imbalanced.

In the ≥50 YOA stratum, the incidence of unsolicited AEs within the 30-day post-vaccination period was similar between HZ/su and placebo groups (46.7% and 46.0%, respectively).

Reviewer comment: *There were no clinically relevant imbalances in unsolicited AEs in the 30-day post-vaccination period reported by subjects ≥50 YOA that were noted by the clinical reviewer that are not discussed elsewhere. The imbalance in Arthralgia was noted primarily in subjects ≥50 YOA.*

Related unsolicited AEs

The incidence of related unsolicited AEs (serious and non-serious) during the 30-day post-vaccination period was higher in the HZ/su group compared to the placebo group (5.5% and 3.1%, respectively). Related adverse events most frequently belonged to the SOC General disorders and administration site conditions (49 subjects, 3.1% in the HZ/su and 19 subjects, 1.2% in the placebo groups), Skin and subcutaneous tissue disorders (14 subjects, 0.9% in the HZ/su and 7 subjects, 0.5% in the placebo groups), and Musculoskeletal and connective tissue disorders (13 subjects, 0.8% in the HZ/su and 2 subjects, 0.1% in the placebo groups). The most frequently reported PTs assessed by investigators as related were Injection site pruritus (12 subjects, 0.8% in the HZ/su and 1 subject, 0.1 in the placebo groups), Influenza like illness (8 subjects, 0.5% in the HZ/su group and 0 subjects in the placebo groups), and Arthralgia (6 subjects, 0.4% in the HZ/su and 2 subjects, 0.1% in the placebo groups), all of which reported more frequently in the HZ/su group.

In the 18 – 49 YOA stratum, incidence of related unsolicited AEs (serious and non-serious) reported during the 30-day post-vaccination period was higher in the HZ/su group (7.7%) than in the placebo group (2.6%). In this age stratum, related unsolicited AEs were most frequently reported in the SOC General disorders and administration site conditions (19 subjects, 4.3% in the HZ/su and 6 subjects, 1.4% in the placebo groups), containing the PTs of Injection site pruritus and ILI.

8.4.5 Clinical Test Results

Not applicable.

8.4.6 Systemic Adverse Events

Solicited AEs were not pooled. Please see the individual studies and summaries of the unsolicited AEs and SAEs above.

8.4.7 Local Reactogenicity

Solicited AEs were not pooled. Please see the individual studies.

8.4.8 Adverse Events of Special Interest

Potential immune-mediated diseases (pIMDs)
The table below shows the number and proportion of subjects in each age group in the TVC in the pooled analysis who reported a pIMD at selected time points.

Table 65. Summary of subjects reporting at least one pIMD and related pIMDs reported during the selected study periods, ISS (TVC)

Adverse Event	HZ/su N=1587 n*	HZ/su N=1587 n	HZ/su N=1587 %	Placebo N=1529 n*	Placebo N=1529 n	Placebo N=1529 %
All pIMDs up to 30 days post-last vaccination	5	5	0.3	3	3	0.2
Related pIMDs up to 30 days post-last vaccination	1	1	0.1	0	0	0.0
All pIMDs up to 365 days post-last vaccination	21	20	1.3	16	16	1.0
Related pIMDs up to 365 days post-last vaccination	4	3	0.2	1	1	0.1

Source: Adapted from 125614/398.0, ISS, Table 37, p. 170
pIMD = potential immune-mediated disease; ISS = integrated summary of safety; TVC = total vaccinated cohort; N = number of subjects with at least one administered dose; n* = number of events; n/% = number / percentage of subjects reporting the symptom at least once

The table below lists the pIMDs up to 365 days following the last vaccination.

Table 66. Summary of pIMDs reported in the HZ/su group as occurring up to 365 days following the last vaccination, event timing, relationship and subject demographics, ISS (TVC)

Study	Age/ Gender	Underlying Disease	pIMD	Last Dose #	Onset Days Post-Dose	Related (Investigator)	Reviewer Assessment of Possible Causal Association	Comments
-002	59 M	Multiple myeloma	Interstitial lung disease	2	0	No	Yes*	
-002	52 M	NHBCL	Autoimmune hemolytic anemia	2	1	No	Yes*	
-002	51 M	Multiple myeloma	Psoriasis	1	9	No	No	Biopsy consistent with drug induced eczema, possibly due to Bactrim
-002	70 M	Multiple myeloma	Psoriasis	1	12	Yes	Yes	20-year history of psoriasis, no alternate plausible cause
-039	50 M	AML	Gout	1	31	No	N/A	Not reported in medical history, 3 months post-chemotherapy, “suspicion of gout,” no recurrence post-dose 2
-039	34 F	NHBCL	Erythema nodosum	2	32	No	Yes*	No alternate plausible cause
-039	66 M	CLL	Autoimmune pancytopenia	2	34	No	No	Present prior to and didn’t worsen after HZ/su
-002	53 M	Multiple myeloma	Hypersensitivity vasculitis	2	46	No	Yes*	Alternate plausible cause not proposed
-002	61 M	NHBCL	Optic neuritis	2	65	No	Yes*	
-002	64 F	Multiple myeloma	Myelitis	2	80	No	No	Due to radiation therapy
-041	26 M	Renal transplant	Gout	2	91	No	N/A	Not reported in history, on tacrolimus
-002	69 M	Multiple myeloma	Cutaneous vasculitis/Arthralgia	2	120/122	Yes	Unlikely*	Not biopsy confirmed, thalidomide started 9 days prior to onset
-002	68 M	NHTCL	Immune thrombocytopenic purpura	2	136	Yes	Unlikely*	Recent (2 weeks) viral infection or “non-remission” NHTCL more likely alternate plausible cause

Study	Age/ Gender	Underlying Disease	pIMD	Last Dose #	Onset Days Post-Dose	Related (Investigator)	Reviewer Assessment of Possible Causal Association	Comments
-041	36 F	Renal transplant	Type I diabetes	2	136	No	No	Pancreatic transplant for baseline medical condition, no reported worsening after HZ/su
-002	63 F	Multiple myeloma	Autoimmune thyroiditis	2	146	No	Unlikely	Positive family history, no alternate plausible cause but long time to onset
-002	65 M	Multiple myeloma	Facial paralysis	2	199	No	Unlikely	No alternate plausible cause but long time to onset
-041	38 M	Renal transplant	IgA nephropathy	2	223	No	No	Recurrence of underlying disease
-002	26 M	Large B Cell Lymphoma	Hemophagocytic lymphohistiocytosis	2	228	No	No	Likely due to underlying disease
-002	57 M	NHBCL	Polymyalgia rheumatica	2	252	No	No	Likely due to underlying disease
-041	51 M	Renal transplant	Gout	2	307	No	N/A	Not reported in medical history, on tacrolimus

Source: Adapted from 125614/398.0, ISS, Table 37, p. 170
pIMD = potential immune-mediated disease; ISS = integrated summary of safety; TVC = total vaccinated cohort; M = male; F = female; NHBCL = non-Hodgkin B cell lymphoma; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; NHTCL = non-Hodgkin T cell lymphoma; N/A = not applicable as no narratives of gout were provided, see discussion below.
* Narrative provided below

In the placebo group, pIMDs with the following PTs were reported up to 365 days following the last vaccination: Autoimmune hemolytic anemia, Autoimmune thyroiditis, Colitis microscopic, Myelitis, Gout (n=2), Type 1 diabetes mellitus, Spondylitis, Systemic scleroderma, Facial paralysis, GBS, IgA nephropathy (n=2), Interstitial lung disease (n=2), and Psoriasis. The one pIMD in the placebo group assessed by investigators as related was GBS.

Three pIMDs in the HZ/su group occurred more than 365 days after last vaccination: VIth nerve paralysis at 396 days post-dose 2, GBS at 420 days post-dose 2, and demyelinating polyneuropathy at 425 days post-dose 2. One pIMD was reported in the placebo group: Facial paralysis at 391 days post-dose 2. Collection of pIMDs beyond 365 days following the last dose was not specified in any trial. These events were not considered related by the investigators.

Reviewer comment: *A similar proportion of subjects reported pIMDs in each vaccination group up to 30 and 365 days following the last vaccination. By PT, no events were reported in more than one subject in the HZ/su group and no subjects in the placebo group. A similar proportion of subjects reported pIMDs in the HZ/su and placebo groups within each age stratum,18 – 49 (5 subjects, 1.1% and 4 subjects, 1.0%, respectively) and ≥50 (15 subjects, 1.3% and 12 subjects, 1.1%, respectively) YOA.*

No narratives were provided for subjects in the HZ/su group who reported gout because gout was added as a pIMD after the conclusion of these studies. This addition was due to a higher frequency of unsolicited AEs of gout in the HZ/su group in the 30-day post-vaccination period in the older adult trials and a possible immune etiology of gout flares. In this sBLA, in the pooled analysis, there was no clinically significant imbalance in gout, which was reported in 5 subjects (3 in the HZ/su group beginning days 31 – 307 post-vaccination and 2 in the placebo group beginning days 14 and 189 post-vaccination).

Although overall events and PTs were balanced between groups, there are several pIMDs the reviewer considers possibly related to vaccination. Given the subject's medical histories and recent or concurrent medical therapies, many of the reported pIMDs have alternate plausible causes. Reviewer assessment was based on biologic plausibility given temporal relationship and judgement that a causal association with vaccine was at least as likely as any alternate plausible cause identified.

Brief narratives for events in which the reviewer assessment differed from the investigator's assessment are described below:

- **Interstitial lung disease (ILD):** A 59 YO man with MM treated with autoHCT who developed a fever the day of dose 2 of HZ/su and was hospitalized with ILD 9 days later. A diagnosis of drug-induced pneumonitis was made bronchoalveolar lavage. The investigator considered the day of onset too soon for a vaccine relationship. Lenalidomide, the investigator's suspected causative agent, had been started the day of HZ/su dose 2. The subject received lenalidomide two additional times during the study without recurrent ILD. The Applicant did not identify an alternate plausible etiology and did not consider the event related to vaccine. ***Reviewer comment:*** *Fever in the immediate post-vaccination period could be reactogenicity with a pulmonary process developing later. There are rare cases reported in the literature of suspected influenza vaccine induced lung injury, mostly in Asia, one that similarly reported fever within hours of vaccination (Numata et al. 2018). In the clinical reviewer's assessment, while it's possible lenalidomide could have caused the ILD in this HZ/su recipient, the timing of exposure with respect to onset of symptoms, which is the same as the timing of*

exposure and onset for dose 2 of HZ/su, and the negative rechallenge make HZ/su as likely a causative agent as lenalidomide. Two subjects in the placebo group in Zoster-002 reported ILD at 52 and 330 days, respectively, post-dose 2). However, in this case a temporal association and no more likely alternate plausible cause suggest a possible causal relationship with vaccine.

- **Autoimmune hemolytic anemia (AIHA):** A 52 YO man with follicular NHBCL treated with autoHCT was hospitalized with AIHA, which is first documented in the narrative 10 days after dose 2 of HZ/su (onset listed as one day post-vaccination when onset of diarrhea is described in the narrative). The investigator considered that the pIMD related to the underlying disease of NHBCL. The Applicant assessed the onset of one day post-vaccination as too short for a vaccine-related pIMD. ***Reviewer comment:*** *Although the subject's NHBCL is an alternate plausible cause, there is no documentation of relapse and AIHA laboratory abnormalities are not documented until 10 days post-vaccination, suggesting a causal relationship with HZ/su vaccination is also possible.*

- **Erythema nodosum:** A 34 YO woman with history of eczema and NHBCL treated with rituximab three months prior to receiving HZ/su, was diagnosed with erythema nodosum with a rash first appearing 32 days after dose 2 of HZ/su. She reported no fever or other complaints, and no biopsy was performed. The investigator confirmed the diagnosis of erythema nodosum, assessed the event as not causally related, and did not consider it a pIMD. ***Reviewer comment:*** *The temporal relationship and lack of an alternate plausible cause suggest a causal relationship of the pIMD with the vaccine can't be ruled out.*

- **Hypersensitivity vasculitis:** A 53 YO man with hematuria, proteinuria, and MM treated with autoHCT and intravenous immune globulin, reported purpura 9 days after dose 1 of HZ/su, nephritis 25 days after dose 2, and was diagnosed with leukocytoclastic vasculitis (PT = Hypersensitivity vasculitis, recorded 46 days post-dose 2). The clinical diagnosis was confirmed with skin biopsy at the time the subject was admitted with hematochezia (4.5 months post-dose 2) attributed to the vasculitis. The pIMD was unresolved when the subject withdrew consent two months later. The investigator did not consider the pIMD vaccine-related and did not provide another cause. The Applicant agreed the pIMD was not caused by the vaccine, noting that cutaneous vasculitis typically occurs within 7-14 days after exposure to a triggering agent. ***Reviewer comment:*** *This subject has a systemic small vessel vasculitis that appears to have presented with purpura nine days after the first dose of HZ/su, progressing to gastrointestinal involvement and possibly renal involvement (though kidney disease is noted at baseline) following the second dose. There is a temporal relationship with vaccination and, although leukocytoclastic vasculitis has been associated with MM, the investigator did not suggest an alternate cause. A causal association with vaccination is plausible. Cutaneous vasculitis and polymyalgia rheumatica were serious pIMDs in the in the Narrow SMQ for vasculitis reported through 365 days post-last vaccination. No placebo group subjects reported serious vasculitides. Leukocytoclastic vasculitis is monitored as part of the enhanced pharmacovigilance since the time of licensure; monitoring was proposed by the Applicant at that time due to one case reported in a 56 YO man 11 days post-dose 1 assessed as related by the investigator.*

- **Optic neuritis (ON):** A 61 YO man with hypertension, diabetes, and NHBCL treated with autoHCT reported decreased visual acuity and visual field disturbances in the right eye 65 days after dose 2 of HZ/su. A neurologist diagnosed anterior ischemic optic neuritis.

Brain magnetic resonance imaging (MRI) showed no evidence of NHBCL and cerebrospinal fluid immunocytometry was normal. Corticosteroids resulted in partial improvement. He received intravenous immune globulin and azathioprine for ON for the remainder of the study, and the event was unresolved. The investigator did not consider this event a pIMD, assessed that it was not related to HZ/su, and identified three causes: "a) ischemic optic neuritis, b) infiltrative optic neuritis, or c) paraneoplasic optic neuritis." The Applicant assessed the ON to be paraneoplastic, as NHBCL has been associated with retinopathies and couldn't be ruled out based on the MRI. ***Reviewer comment:*** *The etiology of the ON is undetermined and optic ischemic neuropathy is in the differential. In the original BLA, three events of optic ischemic neuropathy occurred within 48 days of vaccination within the HZ/su group only; this may represent an additional case. The subject did not have a documented NHBCL relapse to add support to a paraneoplastic etiology. A relationship with study vaccine can't be excluded. Optic ischemic neuropathy is included in the PI for the older adult population and optic inflammatory diseases are monitored as part of the PVP.*

- **Cutaneous vasculitis/Arthralgia:** A 69 YO man with aortic valve incompetence, tricuspid insufficiency, type 2 diabetes mellitus, "exanthema", and MM treated with autoHCT. Nine days after starting an eight-day course of thalidomide and 120 days after receiving the second dose of HZ/su, he presented with edema, exanthema, and atrial fibrillation. CRP was also elevated to 135.7 mg/L (normal: <5 mg/L). When arthralgia began two days later, vasculitis secondary to vaccination or thalidomide was considered by investigators, and prednisolone was started. No skin biopsy was performed. The Applicant considered that the events unlikely to be HZ/su- related. ***Reviewer comment:*** *While an immune-mediated reaction to vaccination can't be ruled out, particularly given the leukocytoclastic vasculitis (above) the long time to onset and alternate plausible cause of thalidomide makes a causal relationship less likely. Atrial fibrillation and other supraventricular tachycardias were reported more frequently in the HZ/su group in the 30-day post-vaccination period in the original BLA, though no imbalance was seen in the IC studies.*

- **Immune thrombocytopenic purpura (ITP):** A 68 YO man whose medical history included psoriasis and NHTCL treated with autoHCT was hospitalized with petechiae and diagnosed with ITP 136 days after dose 2 (platelet count was 3 $x10^9$/L). He reported an upper respiratory tract infection of viral etiology two weeks prior. The investigator identified three possible causes - recent viral infection (most likely), an autoimmune phenomenon of "non-remission state" peripheral T cell lymphoma, or vaccine-related pIMD (less likely, but possible). The Applicant considered a causal relationship of HZ/su unlikely due to the long time to onset, alternate causes, and pre-existing anemia and thrombocytopenia. ***Reviewer comment:*** *ITP has been reported in the literature in association with HZ/su, with the onset of the referenced case occurring 14 days after the first dose of HZ/su (Schmidt and Maitland 2021). While the relationship to vaccination in this case can't be ruled out, the reviewer agrees with the Applicant that the more recent viral infection is the more likely etiology.*

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not applicable.

8.5.2 Time Dependency for Adverse Events

Not applicable.

8.5.3 Product-Demographic Interactions

Please see the evaluation of safety events by age strata in sections 8.4.1 – 8.4.4 and 8.4.8.

With respect to safety in other demographic groups, the studies were not powered to evaluate differences in safety based on demographic groupings, so the clinical significance of any differences noted between groups in the below analyses is unknown. However, there was only minor variability, if any, for the proportions of subjects who reported the various safety events by gender, race and ethnicity.

Deaths: In the HZ/su group, no clinically significant differences were noted among gender, race, and ethnic groups for the proportions of subjects who died up to 30 days and 365 days following the last vaccination and during the whole post-vaccination period.

Serious adverse events (SAEs) and potential immune-mediated diseases (pIMDs): In the HZ/su group, no clinically significant differences were noted among gender and ethnic groups for the proportions of subjects who reported SAEs or among racial or ethnic groups who reported pIMDs up to 30 and 365 days post-last vaccination. The proportion of American Hispanic/Latino subjects reporting SAEs within one year of vaccination tended to be lower in the HZ/su group (19.0%) compared to the placebo group (33.8%), which is likely the due to a low number of American Hispanic/Latino subjects enrolled. There was variability in reports of pIMDs by gender. Females in the HZ/su group tending to report fewer pIMDs compared to females in the placebo group (4 subjects, 0.7% in the HZ/su and 8 subjects, 1.4% in the placebo groups) and males in the HZ/su group tending to report more pIMDs compared to males in the placebo group (16 subjects, 1.6% in the HZ/su and 8 subjects, 0.8% in the placebo groups). This may be due to an overall low number of pIMDs reported in the studies.

Unsolicited adverse events (AEs) reported during the 30-day post-vaccination period: In the HZ/su group, females tended to report AEs at a slightly higher rate than males (49.7% and 44.1%, respectively). Similar to SAEs, the proportion of American Hispanic/Latino subjects reporting unsolicited AEs within 30 days of vaccination tended to be lower in the HZ/su group (49.2%) compared to the placebo group (58.5%) but was similar in the HZ/su group in both vaccination groups. In the HZ/su group the proportions of subjects reporting unsolicited AEs (serious and non-serious) during the 30-day post-vaccination period by race ranged from 36.7% (African race) to 48.8% (Asian race).

Common AEs which were solicited from subjects during the 7-day post-vaccination period: Among HZ/su recipients, the incidence of solicited local and general symptoms was higher in the 18 – 49 YOA group (91.1% and 70.8%, respectively) when compared to the ≥50 YOA group (84.2% and 60.8%, respectively). The proportions of females in the HZ/su group reporting solicited local and general symptoms (89% and 81%, respectively) tended to be higher than males (84% and 73%, respectively). There were no clinically significant differences in the proportions of subjects reporting local and general symptoms by racial group or ethnicity.

8.5.4 Product-Disease Interactions

Please see the individual trial reviews for analysis of safety outcomes based on underlying disease subgroups.

8.6 Safety Conclusions

Generally, the overall proportions of subjects reporting unsolicited AEs, deaths, SAEs, and pIMDs were similar between vaccination groups. Some numerical imbalances between vaccination groups were observed. Arthralgia, a nonserious AE reported more frequently in the HZ/su group in the 30-day post-vaccination period, may be related to reactogenicity and is proposed for inclusion in the PI by the Applicant. Subjects in the HZ/su group also reported more unsolicited AEs of ILI and pneumonia (SAEs of pneumonia were also imbalanced) up to 30 days post-vaccination compared to the placebo group; causal relationship to HZ/su could not be ruled out. A numerical imbalance in febrile neutropenia was also observed. The number of such events was small and occurred primarily in subjects receiving chemotherapy. The imbalance in SAEs of pneumonia was observed in subjects 18 – 49 YOA up to 30 and 365 days post-last vaccination. However, fewer subjects in this age stratum were enrolled and fewer reported SAEs compared to the older age group, and the proportion of subjects reporting such SAEs was low overall.

The integrated safety database did not include some IC populations (for example, non-kidney solid organ transplant, autoimmune disorders). The overall size of the safety database (1,587 subjects receiving at least one dose of HZ/su) is not large enough to identify rare adverse reactions to HZ/su. The IC sub-populations evaluated were heterogeneous and may not be large enough to identify uncommon adverse reactions to HZ/su that may be related to the underlying disease or medication. However, no clear serious safety signal related to vaccination was identified in a diverse group of IC subjects, including younger adults (18 – 49 YOA). The safety data is overall supportive of a favorable risk benefit profile of two doses of HZ/su administered 1 to 2 months apart to IC individuals.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The use of HZ/su in pregnant or lactating women has not been prospectively studied during the development program. Pregnant and lactating women were ineligible to participate in the HZ/su clinical trials, and appropriate contraceptive measures were required to avoid exposure during pregnancy.

There were a total of 17 pregnancy reports in 13 women enrolled in Zoster-002, Zoster-039 and Zoster-041 (8 women with 10 pregnancies in the HZ/su group and 5 women with 7 pregnancies in the placebo group). In all the subjects, exposure to HZ/su or placebo occurred before pregnancy. In the HZ/su group, one elective abortion, no spontaneous abortions, and nine live births were reported. One live birth resulted in a neonatal death (see below) assessed as related to HZ/su by the investigator. In the placebo group, three spontaneous abortions in two women and four live births with no congenital anomalies were reported.

In Zoster-002, which enrolled subjects following autoHCT, seven pregnancies reported in six subjects resulting in seven live births and one elective abortion due to “socioeconomic reasons” were reported in the HZ/su group during the entire study period. Six pregnancies in four subjects resulting in four live births and two spontaneous abortions (one live birth and two spontaneous abortions in one woman) were reported in the placebo group. In the HZ/su group, one subject reported exposure to HZ/su three days prior to her last menstrual period (LMP). The remainder of exposures were reported approximately three months or more prior to the LMPs.

In infants of subjects who received HZ/su the following abnormalities were identified: a clinically insignificant mild enlargement of the right ventricle in the neonate born to the woman with exposure to HZ/su 3 days before LMP, a preterm birth at 29 weeks gestation, and meconium aspiration. Each of these neonates were live births without additional adverse events reported.

In Zoster-039, two pregnancies reported in one subject resulted in two live births with no apparent congenital anomalies with one of the neonates dying soon after birth. No pregnancies were reported in the placebo group.

> Neonatal death: The subject was a 22 YO Asian female with no prior pregnancies with a history of Hodgkin's lymphoma treated with vinblastine, bleomycin, doxorubicin, and dacarbazine completed approximately 4.5 months prior to the first dose of HZ/su. The subject (mother) received the first dose of Hz/su and reported moderate IS swelling. She received the second dose on Study Day 30. She reported adverse events of pyrexia, rhinorrhea, and cough starting 19 days after dose 1 for which she took paracetamol, chlorphenamine, aminophylline and clarithromycin; and pain in her right arm, related to HZ/su dose 2 and lasting 45 days for which she took mefenamic acid and gabapentin (for the first two weeks following her LMP).
>
> Approximately 34 days after her last dose of HZ/su, she reported her last menstrual period (LMP). The Applicant's narrative reports she received concomitant multivitamin supplement (Polybion Forte) from this time and onwards. Antenatal obstetric ultrasounds indicated normal fetal development with no reported congenital anomaly. At 36 weeks of gestation, the subject delivered a live female neonate through normal vaginal delivery. APGAR scores, neonatal dimensions, weight, and other delivery details were not reported. The neonate died 30 minutes after delivery due to breathing difficulty, 307 days after dose 2 of HZ/su. Autopsy was not performed. This event was reported as a fatal SAE.
>
> The Investigator assessed that there was a reasonable possibility that the event (neonatal death) may have been caused by the study vaccine due to subject's exposure before pregnancy or to chemotherapy taken by the subject before conception. The Applicant assessed the relationship to HZ/su as unlikely and more likely due to perinatal asphyxia/hypoxia or infection rather than medications or study vaccine received before conception.
>
> Live birth: This same subject as above went on to deliver a live, healthy male neonate with no apparent congenital anomaly. Last exposure to HZ/su was approximately one year prior to LMP.
>
> ***Reviewer comment:*** *The reviewer agrees with the Applicant that relationship of the neonatal death to HZ/su is unlikely given the timing of exposure and other more likely causes (perinatal respiratory distress or infection. The limited information in the narrative describes a pregnancy that progressed normally until breathing difficulties at birth.*

In Zoster-041, one pregnancy was reported in one subject in the placebo group who had HZ/su exposure approximately 8 months prior to LMP. The pregnancy resulted in a spontaneous abortion at 8 weeks gestation with no apparent congenital anomaly. No pregnancies were reported in the HZ/su group.

Reviewer comment: *The number of pregnancies reported in the clinical trials were few (10 in HZ/su recipients) and a majority of exposures to HZ/su were remote from conception. No adverse events were reported with a clear relationship to HZ/su. As women of child-bearing potential were enrolled and pregnancies were reported, CBER recommends the PI be revised to state the data are insufficient to evaluate the risk of HZ/su in pregnancy, instead of stating there are no data. Please see section 4.3 for a discussion of the non-clinical reproductive toxicity studies.*

As the use of HZ/su in pregnant or lactating women has not been prospectively studied during the development program, at CBER's recommendation, the Applicant proposed to conduct a postmarketing commitment (PMC) observational study (EPI-Zoster-039) utilizing claims data from a distributed research network to evaluate pregnancy exposures to HZ/su. The Applicant plans to conduct a feasibility assessment, identifying HZ/su exposed pregnancies among women with IC conditions during a two-year period. If an adequate number of exposures are identified, a cohort study will be performed to identify and assess pregnancy and infant outcomes from adult women with IC conditions exposed to HZ/su during pregnancy and matched controls. If a cohort study is not feasible, a descriptive analysis will be conducted, describing abnormal pregnancy and infant outcomes among adult women with IC conditions exposed to HZ/su during pregnancy and their infants.

9.1.2 Use During Lactation

No data is available to evaluate the safety of HZ/su during lactation.

9.1.3 Pediatric Use and PREA Considerations

The Applicant requested and will receive a full waiver for assessments in all pediatric age groups. See section 5.4 for details.

9.1.4 Immunocompromised Patients

The entire submission is relevant to the IC population.

9.1.5 Geriatric Use

HZ/su is currently licensed for use in individuals 50 YOA and older, regardless of any immunodeficiency or immunocompromise, and an assessment of safety in subjects 60 – 69 YOA and ≥70 YOA was part of the original BLA. The Applicant provided a safety analysis of IC individuals 65 YOA and older, which is summarized here. In the integrated analysis of the six IC trials, 702 subjects ≥65 YOA were included in the TVC, 337 in the HZ/su group and 365 in the placebo group.

Deaths: In subjects 65 YOA and older, up to 30 days following the last dose of HZ/su, no subjects in the HZ/su group and 3 subjects (0.8%) in the placebo group died. Up to 365 days following the last dose of HZ/su, 33 subjects (9.8%) in the HZ/su group and 38 subjects (10.4%) in the placebo group died.

Serious adverse events (SAEs): In subjects 65 YOA and older, up to 30 days following the last dose of HZ/su, 30 subjects (8.9%) in the HZ/su group and 47 subjects (12.9%) in the placebo group reported SAEs. Up to 365 days following the last dose of HZ/su, 111 subjects (32.9%) in the HZ/su group and 130 subjects (35.6%) in the placebo group reported SAEs.

Reviewer comment: *The proportion of subjects who died and who reported SAEs up to 30 and up to 365 days following the last vaccination and during the whole post-vaccination period (for deaths) was higher in the ≥65 YOA group compared to the 18 – 64 YOA group. There were no clinically relevant differences in deaths, in the proportions of subjects reporting SAEs, or the PTs reported between the HZ/su and placebo group within older age group.*

Potential immune-mediated diseases (pIMDs): In subjects 65 YOA and older, up to 30 days following the last dose of HZ/su, 1 subject (0.3%) in the HZ/su group and no subjects in the placebo group reported a pIMD. The PT for this event was Psoriasis. Up to 365 days following the last dose of HZ/su, 4 subjects (1.2%) in the HZ/su group and 2 subjects (0.5%) in the placebo group reported SAEs. The three additional subjects in the HZ/su group reported arthralgia and cutaneous vasculitis in one subject, autoimmune pancytopenia, and ITP. All the related pIMDs in this age group were reported in the HZ/su group (psoriasis, ITP, and arthralgia and cutaneous vasculitis). The pIMDs in the placebo group in this age group were ILD and facial paralysis.

Reviewer comment: *Few subjects 65 YOA and older reported pIMDs. The small number of subjects enrolled who were 65 and older makes it difficult to draw conclusions about rare events such as pIMDs. No clusters of events were identified in this age group.*

Unsolicited adverse events (AEs) reported during the 30-day post-vaccination period: In subjects 65 YOA and older, up to 30 days following the last dose of HZ/su, 46.3% of subjects in the HZ/su group and 48.5% of subjects in the placebo group reported unsolicited AEs (serious and non-serious). No clinically relevant imbalances were noted by primary SOC or by PT between HZ/su and placebo groups.

Common AEs which were solicited from subjects during the 7-day post-vaccination period: Among HZ/su recipients, the incidence of solicited local symptoms was higher in the 18 – 64 YOA group (88.2%) when compared to the ≥65 YOA group (78.5) and the incidence of general symptoms tended to be higher in 18 – 64 YOA group (77.1%) when compared to ≥65 YOA group (72.1%). Grade 3 local and general symptoms also tended to be higher for the younger age group. In the ≥65 YOA group who received HZ/su, the most commonly reported local symptom was pain (74.2%). Grade 3 pain was reported in 8.6% of HZ/su recipients in this age group. In the ≥65 YOA group who received HZ/su, the most commonly reported general symptoms were fatigue (52.8%) and myalgia (46.3%). Grade 3 fatigue and myalgia were the most commonly reported general symptoms, both reported in 5.2% of HZ/su recipients in this age group.

Reviewer comment: *Overall, the solicited adverse event reporting in subjects ≥65 was consistent with reporting in the overall integrated safety population.*

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

9.2.1 Zoster-041: Evaluation of HZ/su in renal transplant recipients

Study design and eligibility
Zoster-041 was an observer-blind, randomized, placebo-controlled, multi-center, non-IND study designed to evaluate the safety and immunogenicity of two doses of the HZ/su vaccine in subjects ≥18 YOA who had received a renal transplant and were on chronic immunosuppressive/anti-rejection therapy. Planned enrollment was 250 subjects (to yield 200

evaluable subjects) randomized 1:1 into two parallel groups to receive two doses of HZ/su or placebo (lyophilized sucrose cake reconstituted with saline) on a Month 0 (M0) and M1 – M2 schedule; the first dose was scheduled for four to eighteen months after transplantation. There was a minimization procedure to account for the following variables: gender, age (18 – 29, 30 – 49, ≥50 YOA), panel reactive Ab (PRA) score prior to or at the time of transplant (low risk = 0 – 19%, medium risk = 20 – 79%, and high risk = 80 – 100%), and type of maintenance immunosuppressive therapy used at the time of first vaccination [i.e., mycophenolate compounds (MC), calcineurin inhibitors or sirolimus (CIS) and corticosteroids (CS)].

Major eligibility criteria included males and females 18 years of age and older who received an ABO compatible renal transplant (at least 4 months and not more than 18 months prior to first vaccination), who were on stable chronic immunosuppressive therapy for prevention of rejection for a minimum of one month prior to first vaccination with stable renal function [less than 20% variability between the last two creatinine measurements or calculated glomerular filtration rate, or in the opinion of the investigator after review of more than the last two creatinine measurements or calculated glomerular filtration rates] and had no episodes of allograft rejection for 90 days prior to first vaccination. Some pertinent exclusionary conditions were as follows:

- previous vaccination against HZ or varicella or occurrence of HZ or varicella per clinical history within the 12 months preceding the first dose of study product
- pregnant or lactating female
- high risk of allograft rejection (e.g., previous allograft loss due to recurrent primary kidney disease, delayed graft function after transplantation, chronic allograft injury)
- recurring primary kidney disease or primary kidney disease with high incidence of recurrence
- more than one organ transplanted
- PRA score unknown at time of transplant
- systemic autoimmune disease except those localized to the kidney or with diabetic nephropathy
- confirmed or suspected immunodeficiency
- treated with anti-CD20 or other B-cell monoclonal Ab for prevention of allograft rejection within 9 months of first vaccination

There were six planned study visits, including one pre-vaccination visit, two vaccination visits (Visit 1/M0 and Visit 2/M1) and 3 post-vaccination visits (Visit 3/M2, Visit 4/M7 and Visit 5/M13). Two phone contacts were scheduled for safety data collection at Months 7 and 10. Cases of suspected HZ were collected and recorded during the study from Month 0 to study end. Blood sampling for humoral immunogenicity assessments (anti-gE Ab assessments as measured by ELISA) and evaluation of anti-major histocompatibility complex (MHC) Abs were scheduled for collection at visits 1 through 5 for processing at a central laboratory to allay concerns regarding inter-laboratory variability; samples for assessment of CMI response [via intracellular cytokine staining by evaluation of the frequency of CD4 T cells responding to culture medium or antigens (gE peptide pool) secreting cytokine molecules involved in immunity such as IFN-γ, IL-2, TNF-α and CD40L] were to be collected from a sub-cohort of subjects (38 subjects/group to yield 30 evaluable subjects/group) at designated sites at Visits 1, 3, and 5. Total study participation time/subject was approximately 13 months.

<u>Objectives and endpoints</u>
The co-primary objectives of the study were:

- To evaluate the VRR (see definition in section 6.1.9) for anti-gE humoral immune

responses at M2 following a 2-dose administration of HZ/su as compared to placebo in all subjects. The objective would be met if the LB of the 95% CI of the VRR for anti-gE Ab concentration at M2 in the HZ/su vaccine group is at least 60%.
- To evaluate the safety and reactogenicity of the HZ/su vaccine as compared to placebo up to 30 days after last vaccination in all subjects.

Secondary objectives included the following:
- To evaluate the anti-gE humoral immune response at M2 following a 2-dose administration of HZ/su as compared to placebo in all subjects. The objective would be met if the LB of the 95% CI of the GMR (HZ/su over placebo) for anti-gE Ab concentrations at M2>3.
- To characterize the anti-gE humoral immune responses at Ms 0, 1, 2, 7 and 13 in all subjects.
- To evaluate the following regarding gE-specific CD4+ CMI in a subcohort of subjects:
  - VRR at M2 following 2 doses of HZ/su; the objective would be met if the LB of the 95% CI for gE-specific CD4+ T cell frequencies at M2 in the HZ/su group is >50%.
  - gE-specific CD4+ T cell mediated responses at M2 following two doses of HZ/su compared to placebo; the objective would be met if the LB of the 95% CI of the GR (HZ/su over placebo) for gE-specific CD4+ T cell frequencies at M2>1.
  - gE-specific CD4+ T cell mediated immune responses at M 0, 2 and 3 in the HZ/su and placebo groups

A tertiary safety objective was to describe the development of de novo and modification of anamnestic alloantibodies to MHC antigens as anti-HLA antibodies, donor-specific antibodies and other, and anti-MHC class I-related Chain A antibodies from first vaccination until study end in all subjects.

Reviewer comment**:** *The objectives, eligibility criteria, and study design presented here were established after CBER's courtesy r*eview *of the original non-IND protocol; CBER provided comments and recommendations on March 22, 2013. That communication included comments about a) enrollment criteria (e.g., no establishment of minimum time from renal transplant to enrollment), b) endpoints (e.g., lack of a clinical endpoint), and c) safety monitoring (e.g., lack of monitoring of donor-specific or non-donor specific Abs, lack of monitoring of clinical events other than biopsy-confirmed allograft rejection, such as acute or chronic allograft dysfunction). Contributing to CBER's safety monitoring concerns, development of de novo HLA and donor-specific antibodies were detected after administration of the AS03 adjuvanted H1N1 vaccine in small uncontrolled studies enrolling renal transplant subjects (Katerinis et al. 2011; Fairhead et al. 2012). The Applicant revised the protocol addressing some of CBER's comments above.*

The co-primary study endpoints were as follows:
- Anti-gE humoral immunogenicity in all subjects – vaccine response (VR) for anti-gE humoral immunogenicity measured by ELISA at M2
- Occurrence of AEs
  - Occurrence, intensity and duration of local solicited AEs and occurrence, intensity, duration and relationship to vaccination of general solicited AEs within 7 days after each vaccination
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during the 30 days after each vaccination
  - Occurrence and relationship to vaccination of all SAEs and occurrence of pIMDs from first vaccination up to 30 days after last vaccination
  - Occurrence of biopsy-proven renal allograft rejection from first vaccination up to 30

days after last vaccination
- Allograft function as measured by serum creatinine from the first vaccination up to 30 days after last vaccination

Secondary endpoints included the following: anti-gE humoral immunogenicity as measured by ELISA at M 0, 1, 2, 7 and 13, gE-specific CD4 T cell mediated immunogenicity in the CMI subcohort including frequencies of gE-specific CD4+ T cells and vaccine response for gE-specific CD4+ T cells expressing at least two activation markers at specific time points, occurrence and relationship to vaccination of all SAEs from 30 days after last vaccination to study end, occurrence of pIMDs from 30 days after last vaccination to study end, biopsy-proven renal allograft rejection and allograft function as measured by serum creatinine from 30 days after last vaccination until study end. The tertiary endpoint was anti-MHC Ab responses: quantification of anti-MHC Ab response as anti-MHC class I-related Chain A Abs and anti-HLA Abs (donor and non-donor-specific) characterized as de novo or anamnestic responses from the first vaccination until study end.

Reviewer comment: *HZ VE was not an endpoint in this study.*

Analysis populations
The primary population for the analyses of safety were performed on the TVC, which consisted of all vaccinated subjects (subjects with at least one vaccination) according to the vaccine received. The primary populations for the analyses of immunogenicity were performed on the ATP cohorts for immunogenicity; these were subjects who met eligibility criteria, who complied with the procedures and intervals as defined in the protocol, and from whom data concerning immunogenicity endpoints were available.

Study dates
Study initiation date: March 20, 2014
Study completion date: April 13, 2017

Demographics
The demographic composition of the TVC is presented below.

Table 67. Summary of demographic characteristics, Zoster-041 (TVC)

Characteristic	HZ/su N=132 n (%)	Placebo N=132 n (%)	Total N=264 n (%)
Age (years) at dose 1			
Mean (SD)	52.3 (12.5)	52.4 (12.8)	52.4 (12.6)
Median (min, max)	53.5 (20, 82)	53.5 (21, 79)	53.5 (20, 82)
Gender			
Female	38 (28.8)	41 (31.1)	79 (29.9)
Male	94 (71.2)	91 (68.9)	185 (70.1)
Ethnicity			
Hispanic or Latino	13 (9.8)	7 (5.3)	20 (7.6)
Not Hispanic or Latino	119 (90.2)	125 (94.7)	244 (92.4)

Characteristic	HZ/su N=132 n (%)	Placebo N=132 n (%)	Total N=264 n (%)
Geographic Ancestry			
African Heritage/African American	3 (2.3)	1 (0.8)	4 (1.5)
American Indian or Alaskan native	0 (0.0)	0 (0.0)	0 (0.0)
Asian, Central/South Asian heritage	1 (0.8)	2 (1.5)	3 (1.1)
Asian, East Asian heritage	20 (15.2)	22 (16.7)	42 (15.9)
Asian, Japanese heritage	0 (0.0)	1 (0.8)	1 (0.4)
Asian, South East Asian heritage	10 (7.6)	3 (2.3)	13 (4.9)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White, Arabic/North African heritage	2 (1.5)	2 (1.5)	4 (1.5)
White, Caucasian/European heritage	88 (66.7)	97 (73.5)	185 (70.1)
Other	8 (6.1)	4 (3.0)	12 (4.5)

Source: 125614/398.0, Zoster-041 CSR, Table 23, p. 150
TVC = total vaccinated cohort; N = total number of subjects; n/% = number / percentage of subjects in a given category; SD = standard deviation

The majority of subjects in the TVC were Caucasian and not of Hispanic or Latino ethnicity. The mean and median ages overall were 52.4 and 53.5 years, respectively. The minimum and maximum ages in the treatment groups were 20 and 21 years and 82 and 79 years in the HZ/su and placebo groups, respectively. There were more males than females participating. Of subjects in the TVC, 14 (5.3%) were <30 YOA and 83 (31.4%) were ≥30 and <50 YOA. Although not presented here, the demographic composition of the ATP cohort for humoral immunogenicity was similar to that of the TVC.

Reviewer comment: *The demographic composition of the TVC was similar between vaccination groups.*

The study population was over 70% White/Caucasian of European heritage and only 1.5% were of African/African American heritage. This is dissimilar to the demographics of kidney transplant recipients in the US. According to the Organ Procurement and Transplantation Network, from January 1, 1988 to June 30, 2019, 55.3% of organ transplant recipients were Caucasian/White and 24.1% were African American/Black.

The Applicant also provided a summary of demographic characteristics by rejection risk according to PRA/cPRA score. In the TVC, 234 of 264 (88%) were of low rejection risk, 25 of 264 (9.5%) were of medium rejection risk and 5 of 264 (1.9%) were of high rejection risk.

Reviewer comment: *Of US adult kidney transplant recipients in 2014, 14.3% had PRA/cPRA scores from 20 up to 80 (medium rejection risk) and 12.5% had a PRA/cPRA score of ≥80 (high rejection risk). The study population differs from the adult renal transplant population in the US with regard to the proportions of subjects at higher risk of rejection as measured by PRA/cPRA scoring (Hart et al. 2016).*

The demographic breakdown by type of immunosuppressive therapy was as follows (≤2 subjects had maintenance therapy not reflected here):

- CIS + CS + MC – 202/262 (77.1%)
- CIS + MC – 45/262 (17.2%)
- CIS + CS – 15/262 (5.7%)

Reviewer comment: *Post-transplant immunosuppressive therapy is diverse and complex, but*

triple therapy (corticosteroid, calcineurin inhibitor and an antimetabolic agent) is a commonly used regimen in the US.

Disposition and exposure

Of the 264 subjects in the TVC, 260 completed the study and 2 subjects from each group were withdrawn from the study, 3 due to an AE or SAE. In the HZ/su group, both subjects were withdrawn due to an AE or SAE. One subject was withdrawn because of a non-serious AE of herpes zoster which occurred prior to dose 2 and the other subject, a 72 YO male reported an SAE (judged unrelated) of purulent meningitis 17 days after the second vaccination and died 26 days later.

The majority (96.2%) of subjects in the total vaccinated cohort (TVC) received both vaccinations; ten subjects did not receive a second vaccination (6 subjects, 4.5% in the HZ/su and 4 subjects, 3.0% in the placebo groups). Reasons for discontinuation from vaccination in the HZ/su group were the following: the subject who reported HZ prior to a second dose, 3 subjects who were deemed ineligible by the investigator due to protocol violations, 1 subject who decided to discontinue due to a non-serious AE of fever and 1 subject who did not receive the second dose per investigator due to a serious, unrelated SAE of urosepsis.

Overall, 90.9% of subjects in the TVC (240/264) were included in the ATP cohort for humoral immunogenicity. The most common reason for exclusion from this cohort was protocol violations.

Reviewer comment: *The proportions of subjects excluded from the ATP cohort for humoral immunogenicity and the reasons for exclusion were balanced between treatment groups.*

Safety results – solicited AEs

Solicited local (IS pain, redness and swelling) and general (fever, headache, fatigue, GI symptoms, myalgia, and shivering) events were recorded on a diary card for 7 days after each vaccination. Over 99% of TVC subjects in both treatment groups returned symptom sheets after each vaccination. The proportion of subjects in the TVC reporting at least one any grade or Grade 3 solicited AE (overall/subject) with both doses considered during the 7-day solicited AE reporting period is below.

Table 68. Percentage of subjects reporting at least one solicited AE overall/subject by treatment group in the 7-day reporting period, Zoster-041 (TVC)

	HZ/su	Placebo
≥1 solicited AE	92.4%	56.8%
≥1 Grade 3 solicited AE	15.3%	8.3%
≥1 solicited local AE	87.8%	9.1%
≥1 Grade 3 solicited local AE	10.7%	0.0%
≥1 solicited general AE	68.7%	55.3%
≥1 Grade 3 solicited general AE	9.9%	8.3%

Adapted from 125614/398.0, Zoster-041 CSR, Tables 8.3 and 8.4, pp. 419 – 420
AE = adverse event ; TVC = total vaccinated cohort

Overall per subject, the most commonly reported solicited local event in the HZ/su group was pain. With both doses considered, overall per subject, 87.0% of subjects in the HZ/su group reported any grade pain as compared to 8.3% of subjects in the placebo group; of the HZ/su subjects, 9.9% reported Grade 3 pain. Any grade (Grade 3) redness and swelling were reported (with both doses considered) by 25.2% (0.8%) and 11.5% (0.8%) of subjects in the HZ/su group, respectively. The median duration of local symptoms in the HZ/su group (depending on

the symptom) was 3.0 to 4.0 days.

The Applicant collected general events that were to be solicited at baseline (one week before vaccination) to help assess the relationship between receipt of HZ/su and reporting of these events post-vaccination. Although the proportions of subjects reporting Grade 3 general events pre-vaccination were low (<4% for any specific general symptom in both treatment groups, a substantial number reported any grade fatigue (37.9% HZ/su group, 40.9% placebo group), GI symptoms (22.7% HZ/su group, 19.7% placebo group), headache (25.0% HZ.su group, 25.8% placebo group), and myalgia (21.2% HZ/su group, 25.8% placebo group) pre-vaccination.

Reviewer comment: *General AEs that were solicited on the 7-day diary card were frequently reported before vaccination; this attests to the overall morbidity of the study population*.

Post vaccination, overall per subject with both doses considered, any grade myalgia was the most frequently reported solicited general AE (reported by 49.6% and 23.5% of HZ/su and placebo recipients, respectively). Overall per subject with both doses considered, any grade fatigue (47.3% HZ/su group, 40.2% placebo group), headache (33.6% HZ/su group, 25.8% placebo group), and shivering (22.1% HZ/su group, 12.1% placebo group) were reported by more than 20% of the HZ/su group in the 7-day post-vaccination period. Overall per subject considering both doses, the only Grade 3 solicited general event that was reported by >5% of subjects during the 7-day post-vaccination period was myalgia, reported by 6.9% of subjects. Fever, defined as body temperature ≥37.5°C (all routes except rectal) was reported overall per subject during the 7-day post-vaccination period (both doses considered) by 16.0% and 3.8% of subjects in the HZ/su and placebo groups respectively. Overall by subject considering both doses, body temperature ≥39°C was reported by one subject (0.8%) and no subjects in the HZ/su and placebo groups, respectively. There was a trend for higher proportions of subjects in the HZ/su group reporting any grade shivering after dose 2 (18.4%) as compared to dose 1 (7.6%) and any grade fever after dose 2 (12.0%) as compared to dose 1 (6.1%). The median duration of general symptoms in the HZ/su group (overall/dose) was from 1.0 to 3.0 days.

Overall per subject, and considering both doses during the 7-day reporting period, the proportions of subjects in the HZ/su group reporting any solicited local symptom (91.7% vs. 85.5%) and any solicited general symptom (77.1% vs. 63.9%) any Grade 3 general symptoms (14.6% vs. 7.2%) trended higher for subjects 18 – 49 YOA compared to subjects ≥50 YOA. The proportions of subject reporting Grade 3 local symptoms were comparable between the 18 – 49 YOA (10.4%) and ≥50 YOA (10.8%) groups.

<u>Safety results – unsolicited AEs</u>
Unsolicited AEs (including SAEs) were collected on a diary card and recorded during the 30-day post-vaccination periods; tabulations of events were provided by MedDRA SOC and PT. During this period 38.6% of TVC subjects in the HZ/su group and 33.3% of subjects in the placebo group reported the occurrence of at least one unsolicited AE of any grade. The SOC Infections and infestations had the highest proportion of subjects reporting at least one AE contained in the SOC; 18.9% and 16.7% of subjects in the HZ/su and placebo groups, respectively, reported at least one AE in that SOC. The most commonly reported AE in the HZ/su group during the reporting period was urinary tract infection, reported by 4.5% of subjects in the HZ/su group and 2.3% of subjects in the placebo group. The most commonly reported single AE in the placebo group during that period was nasopharyngitis reported by 2.3% of subjects in the HZ/su group and 3.8% of subjects in the placebo group. One case of HZ was reported in each group during this period.

Grade 3 non-serious unsolicited AEs were reported by 3.8% (n=5) of subjects (who reported 6 events by PT) in the HZ/su group and 2.3% (n=3) of subjects (who reported 3 events by PT) in the placebo group during the 30-day post-vaccination reporting periods. No single event by PT was reported more than once in each group. The events reported in the HZ/su group were peripheral swelling and pain in extremity in a single subject, erysipelas, herpes zoster, back pain, and somnolence. The peripheral swelling (verbatim terms = hand and arm swelling) and pain in extremity in a single subject were both assessed as related by the investigator.

Overall, 34 subjects (25.8%) in the HZ/su group and 29 subjects (22.0%) in the placebo group reported at least one unsolicited symptom with a medically attended visit during the 30-day post-vaccination period. The most frequently reported unsolicited AE with a medically attended visit during this period in both groups was urinary tract infection, reported by 4 subjects (3.0%) in the HZ/su group and 3 subjects (2.3%) in the placebo group.

Safety results – SAEs

SAEs were collected from first vaccination until study end. From first vaccination up to 30 days post-last vaccination, 6 subjects (4.5%) in the HZ/su group and 5 subjects (3.8%) in the placebo group reported 6 events (in each group). The SAEs reported in the HZ/su group were gastritis, influenza, Klebsiella sepsis, meningitis, and pyelonephritis acute (n=2). The SAEs reported in the placebo group were diabetic ketoacidosis and type 2 diabetes mellitus in one subject, and vertigo, pyelonephritis acute, benign gastrointestinal neoplasm, and renal impairment. None were judged causally related to study products.

From 30 days post-last vaccination until study end, 21 subjects (15.9%) in the HZ/su group and 29 subjects (22.0%) reported at least one SAE. Subjects in the HZ/su group reported 30 SAEs classified by PT and subjects in the placebo group reported 43 SAEs classified by PT. PTs in the SOC Infections and Infestations were reported most often; 10.6% of subjects in each group reported at least one event in this SOC. No SAEs in subjects in the HZ/su group were judged causally related to study product.

Reviewer comment**:** *Due to immunosuppression, subjects with solid organ transplants are more susceptible to infections, including severe infections, than immunocompetent subjects (Berger and Pagalilauan 2020).*

Two subjects died during the study. The deaths were considered unrelated to study product.

- HZ/su group - A 72 YO male subject (on tacrolimus, prednisone and MC as immunosuppressive therapy) with a concurrent medical history which included coronary arteriosclerosis, hyperlipidemia, hyperuricemia, steroid induced diabetes and pulmonary hypertension was reported as having purulent meningitis 17 days after receiving the second dose of HZ/su. His course was complicated by pulmonary sepsis and *Clostridium difficile* colitis. He was treated with ceftriaxone, ampicillin, vancomycin, meropenem and metronidazole. He died 26 days after the onset of the AE.
- Placebo group - A 56 YO male subject died at home 229 days after receiving the second dose of placebo; the autopsy revealed vascular graft thrombosis, myocardial infarction, and coronary artery disease.

Reviewer comment: *The narrative and case report form for the subject in the HZ/su group who reported meningitis was reviewed. No other cases of meningitis were reported within 30 days of last vaccination in the HZ/su group as per the ISS; although unlikely, a relationship to vaccination cannot be fully ruled out due to temporal association. See a discussion of the proportions of subjects reporting infectious AEs, including meningitis post-vaccination in the ISS (section 8.4).*

Safety results - AESIs

Potential immune-mediated inflammatory diseases (pIMDs), biopsy-proven renal allograft rejection, changes in allograft function and increases/changes in anti-MHC antibodies were collected and recorded during the study.

No pIMDs were reported from first vaccination up to 30 days post-last vaccination. From 30 days post-last vaccination until study end, 4 subjects (3.0%) in the HZ/su group reported 4 pIMDs and 2 subjects (1.5%) in the placebo group reported 2 pIMDs. The pIMDs in the HZ/su group were 2 episodes of gout (reported by 2 subjects, 91 and 307 days after second vaccination), IgA nephropathy and type 1 diabetes mellitus (reported 136 days after dose 2). Two cases of IgA nephropathy were reported in the placebo group.

Reviewer comment: *Please see discussion of pIMDs across studies in the ISS (section 8.4.8).*

Biopsy-proven allograft rejection was reported from Visit 1 to study end. From first vaccination up to 30 days after last vaccination, 0 subjects in the HZ/su group and 3 subjects in the placebo group had renal biopsies; all were negative for allograft rejection. From 30 days after last vaccination to study end, 12 (9.1%) of HZ/su recipients and 13 (9.9%) of placebo recipients had renal biopsies negative for allograft rejection and 4 (3.0%) HZ/su recipients and 7 (5.3%) placebo recipients had biopsies reported as biopsy-proven rejection. The 4 cases of rejection in 4 subjects in the HZ/su group had an onset on study days 159, 164, 178 and 223 and were diagnosed or assessed as borderline acute cellular rejection, subclinical borderline rejection, acute cellular rejection, and recurrent IgA nephropathy and focal thrombotic microangiopathy, respectively.

Reviewer comment: *Monitoring for a longer period than 13 months after last vaccination to assess for late allograft failure would have provided additional support for the safety of the product in this population.*

Creatinine measurements were recorded as a proxy for renal allograft function and pre-vaccination values were compared to post-vaccination values. The serum creatinine measures were obtained as per local surveillance protocols and/or for clinical indications; the timing of the blood draws for creatinine measurement were not pre-specified for collection by the Applicant at specific time points relative to vaccination. The numbers and proportions of subjects with an increase in serum creatinine in the TVC up to 30 days post-last vaccination and from 30 days post-last vaccination to study end is presented below.

Table 69. Fold increases of creatinine measurements from baseline, Zoster-041 (TVC)

Fold Increase From Baseline	Reported up to 30 Days After Last Vaccination HZ/su N=113 n (%)	Reported up to 30 Days After Last Vaccination Placebo N=107 n (%)	Reported from 30 Days After Last Vaccination to Study End HZ/su N=130 n (%)	Reported from 30 Days After Last Vaccination to Study End Placebo N=132 n (%)
≥1.20 fold	5 (4.4%)	7 (6.5%)	17 (13.1%)	22 (16.7%)
≥1.50 fold	0 (0%)	1 (0.9%)	4 (3.1%)	3 (2.3%)
≥1.75 fold	0 (0%)	1 (0.9%)	3 (2.3%)	1 (0.8%)
≥2 fold	0 (0%)	1 (0.9%)	2 (1.5%)	0 (0%)

Adapted from 125614/398.0, Zoster-041 CSR, Tables 8.61 and 8.62, p. 480
TVC = total vaccinated cohort; N = Number of subjects with the data available pre- and post- vaccination; n/% = number / percentage of subjects reporting an increase in creatinine from pre vaccination at least once.
The mean of the last 10 available values before vaccination is used as baseline value.

Reviewer comment: *Although the data that are presented do not indicate a safety signal of worsening renal function as measured by creatinine, passive reporting of the creatinine results, which were collected inconsistently, limits the interpretability and utility of the between-group comparisons of these results.*

Blood draws for assessment of changes in and/or de novo generation of anti-MHC Ab (donor-specific and non-donor specific) was pre-specified for collection at study visits 1 through 5; these assessments were not performed by the Applicant. Therefore, there are limitations to interpretation of the anti-MHC antibody results provided:

- Few subjects overall had sampling for anti-MHC antibody testing (testing was limited primarily to academic centers with interest in the kinetics of such antibodies).
- As the samples were processed at local laboratories, there may have been inter-laboratory variation in sample processing.
- Baseline sampling (to compare to post-vaccination antibody results) was not performed just prior to first vaccination, but months before, generally pre-transplant, at transplant, or in the immediate post-transplant period.
- Post-vaccination sampling for anti-MHC antibodies were obtained at various timepoints after vaccination (instead of at fixed timepoints after vaccination).

Only 11 subjects total (10 in the HZ/su group and 1 in the placebo group) had anti-MHC antibody testing from first vaccination to study end; of the 10 subjects in the HZ/su group who had such testing during the study, 5 subjects had qualitative testing only. Results include the following:

- De novo antibody generation: From the period of first vaccination up to 30 days post-last vaccination, five subjects (four in the HZ/su group and one in the placebo group) had local lab anti-MHC testing; two subjects (one in each treatment group) had detectable quantitative de novo anti-MHC antibodies. Local anti-MHC Ab testing from 30 days post-last vaccination to study end was limited to 9 subjects (all in the HZ/su group, 3 of whom were also previously tested in the 30-day post-last vaccination time period). Of these nine subjects in the HZ/su group, six were confirmed to have developed de novo anti-MHC antibodies (two by qualitative testing only).
- Increases in anti-MHC antibody: Of the 5 subjects in the HZ/su group who had

quantitative anti-MHC antibody testing, 3 had increases in memory anti-MHC antibodies (these 3 subjects were tested during the period from 30 days post-last vaccination to study end).

Reviewer comment: *The very limited data provided and non-systematic collection of anti-MHC Abs do not allow for meaningful between-group comparisons.*

Cases of HZ

Ten subjects reported suspected cases of HZ, three in the HZ/su group and seven in the placebo group. An additional subject in the placebo group reported a non-serious AE of varicella. The three suspected cases in the HZ/su group were non-serious. One was reported 5 days after dose 1 and the other two were reported 264 and 353 days after dose 2. Their anti-gE Ab concentrations at Month 0 and Month 2 were 2187 (M0) and 4206 (M2) mIU/mL and 2202 (M0) and 4366 mIU/mL (M2), respectively.

Reviewer comment: *Per protocol, suspected HZ cases were not confirmed by PCR, nor were cases adjudicated by external experts.*

Select immunogenicity results

Seropositivity rates and pre- and post-vaccination GMCs for anti-gE Ab as measured by ELISA are presented below on the Adapted ATP cohort for humoral immunogenicity. At baseline, 96.7% (117/121) of subjects in the HZ/su group and 98.3% (117/119) of subjects in the placebo group were seropositive for anti-gE antibody. At each time point (M2, M7 and M13), there was one subject in the HZ/su group who was seronegative (anti-gE Ab <97 mIU/mL).

In the HZ/su group at baseline, M1, M2, M7 and M13, the GMCs (95% CI) were 1354.4 (1118.3, 1640.4), 9530.5 (7111.3, 12772.7), 19163.8 (15041.5, 24416.0), 13066.7 (10291.5, 16590.4) and 8545.1 (6753.7, 10811.5) mIU/mL respectively, while GMCs in the placebo group during those time points ranged from 1489.4 – 1572.7 mIU/mL. Anti-gE Ab GMCs in the HZ/su group trended higher for younger (18 – 49 YOA) as compared to older (≥50 YOA) HZ/su recipients at these timepoints.

The MGIs (95% CI) of anti-gE Ab concentrations by ELISA at M1, M2, M7 and M13 over baseline in the HZ/su group were 7.0 (5.4, 9.2), 14.1 (11.0, 18.1), 9.8 (7.7, 12.5) and 6.4 (5.1, 8.0), respectively. The MGIs in the placebo group were 1.0 for each time point.

The primary immunogenicity objective for the VRR for anti-gE Ab was met as the LB of the 95% CI of the VRR for anti-gE Ab concentrations at M2 (after second vaccination) in the HZ/su group was 71.9%, above the pre-specified LB of >60%. The VRRs (95% CI) at M1, M2, M7 and M13 in the HZ/su group were 63.6% (54.4%, 72.2%), 80.2% (71.9%, 86.9%), 75.5% (66.3%, 83.2%) and 66.7% (57.1%, 75.3%), respectively.

Reviewer comment: *Humoral responses were highest at M2.*

A secondary objective related to anti-gE Ab concentrations was met as the LB of the 95% CI of the GMR (HZ/su over placebo) for anti-gE Ab concentrations at M2 (after second vaccination) was 10.9, over the pre-specified LB of >3. The adjusted GMR was 14.0 (95% CI: 10.9, 18.0).

The following secondary objectives related to CMI responses were assessed on the ATP cohort for CMI. The secondary objective with respect to the VRR of gE-specific CD4 T cell frequencies was met because the LB of the 95% CI of the VRR for gE-specific CD4 T cell frequencies in the HZ/su group at M2 (after second vaccination) was 51.3%, above the pre-specified LB of >50%. The observed VRR (95% CI) was 71.4% (51.3%, 86.8%). The secondary objective related to the GMR was met as the LB of the 95% CI of the GMR (HZ/su over placebo) with regard to gE-specific CD4 T cell frequencies at M2 (after second vaccination) >1; the observed GMR (95% CI) was 17.3 (5.9, 50.4).

Reviewer comments: *Both cellular and humoral immune responses to HZ/su were demonstrated in this study and the primary immunogenicity objectives met.*

Conclusion *- Zoster-041 was a small safety and immunogenicity study, in which there was a lack of systematic monitoring of some specific safety endpoints. However, there were no between-group imbalances in biopsy-confirmed allograft rejection during the 13-month study and immune responses were demonstrated post-HZ/su vaccination. Combined with the VE, safety, and immunogenicity data from Zoster-002 and Zoster-039, the available data from Zoster-041 support effectiveness and a favorable risk/benefit assessment of the use of the vaccine in this population.*

9.2.2 Zoster-028: Evaluation of HZ/su in subjects with solid tumor malignancies on chemotherapy

Study design and eligibility

Zoster-028 was an observer-blind, randomized, placebo-controlled multi-center, multi-country, non-IND study designed to evaluate the safety and immunogenicity of two doses of the HZ/su vaccine in subjects ≥18 YOA who had been diagnosed with a solid tumor and who were receiving or about to receive chemotherapy. Planned enrollment was 232 subjects to be randomized 1:1 into two parallel groups (HZ/su and placebo) to receive two doses of HZ/su or placebo (lyophilized sucrose case reconstituted with saline) on a Month 0 (M0) and M1 – M2 schedule; timing of the second dose was flexible to allow for chemotherapy scheduling. Subjects were also stratified by timing of chemotherapy in a 4:1 ratio (PreChemo:OnChemo). For the PreChemo group, the first vaccination was scheduled from 10 days up to 1 month prior to chemotherapy. The OnChemo group was scheduled to have the first vaccination at the start of a first or second round of chemotherapy. The second dose of study product was to be scheduled between 1 – 2 months after the first dose and at the start of a round of chemotherapy.

Reviewer comment: *The Applicant's stated rationale for inclusion of two groups with different timings of vaccination with respect to chemotherapy (PreChemo and OnChemo) was based on unpublished data indicating that vaccination* (b) (4) *.*

Male or female subjects ≥18 YOA were study eligible if they:

- had been diagnosed with one or more solid tumors (i.e., not a hematologic malignancy),

- were receiving or were to receive a cytotoxic or immunosuppressive chemotherapy (such that the study vaccine could be administered, at the latest, at the start of the second cycle of chemotherapy),
- had a life expectancy of >1 year.

Subjects were excluded if they:

- were receiving only "newer, more targeted therapies (e.g., trastuzumab)",
- had chronic administration of (or planned administration of) systemic corticosteroids (e.g., prednisone ≥20 mg/day or equivalent for ≥14 days),
- had previous vaccination against HZ or varicella,
- occurrence of varicella or HZ within 12 months of first vaccination,
- had HIV by history,
- were pregnant or lactating females.

One pre-vaccination, five on-study visits and two phone contacts (At Months 5 and 9) were planned. Visits 1/Month 0 and 2/Month 1 were vaccination visits, with the Visit 2 allowed within 1 – 2 months of Visit 1. Visit 3 (generally Month 2) occurred one month after the second vaccination. Visit 4 occurred within Months 4 – 13 and was scheduled to accommodate a blood sampling at the start of the last cycle of chemotherapy (e.g., if Visit 4 ended up occurring at Months 5, 9 or 13). Visit 5 was the last scheduled visit at approximately Month 13 (12 months after last vaccination). Blood samples were drawn on all subjects for assessment of humoral immune response (anti-gE Ab as measured by ELISA). Blood samples to evaluate CMI response were drawn from a sub-cohort of PreChemo subjects at selected sites (target of 76 subjects to yield 30 evaluable subjects/group) with access to a peripheral blood mononuclear cell processing facility at Visits 1, 2, 3 and 5. CMI was evaluated via intracellular cytokine staining by evaluation of the frequency of CD4 T cells responding to culture medium or antigens (gE peptide pool) secreting cytokine molecules involved in immunity such as IFN-γ, IL-2, TNF-α and CD40L. Total study participation time per subject was approximately 13 months.

Reviewer comment: *The size of the study population was very small. As the types of solid tumors and the therapeutic options and treatment regimens are diverse, the information provided from the study may be limited in terms of extrapolation to the various sub-populations of subjects with solid tumor malignancies including those not on traditional chemotherapy.*

Objectives and endpoints

The co-primary objectives were as follows:

- To evaluate anti-gE humoral immune responses at M2, following administration of two doses of HZ/su as compared to placebo in subjects with solid tumors receiving chemotherapy (PreChemo groups only). The objective would be met if the LB of the 95% CI of the GMR (HZ/su PreChemo group over placebo PreChemo group) for anti-gE Abs by ELISA >3.
- To evaluate the safety and reactogenicity following administration of HZ/su as compared to placebo up to 30 days post-last vaccination in subjects with solid tumors receiving chemotherapy.

There were 5 secondary immunogenicity objectives (paraphrased):

- Evaluation VRR (see definition in section 6.1.9) for anti-gE humoral responses as measured by ELISA at M2 following 2 doses of HZ/su in the PreChemo group. The objective would be met if the LB of the 95% CI of the VRR at Month 2 was >60%.
- Evaluation of gE-specific CD4 T cell responses at M2 following 2 doses of HZ/su as compared to placebo in the CMI sub-cohort. The objective would be met if the LB of the 95% CI of the GMR (HZ/su PreChemo group over placebo PreChemo group) at M2>1.
- Evaluation of VRR for gE-specific CD4 T cell mediated immunogenicity at M2 after 2 doses of HZ/su in subjects in the CMI sub-cohort. The objective would be met if the LB of the 95% CI of the VRR for the gE-specific CD4 T cell frequencies is >50%.
- Evaluation of anti-gE humoral immune response at M2 after two doses of HZ/su as compared to placebo in all subjects. The objective would be met if the LB of the 95% CI of the GMR (HZ/su group over placebo group) for anti-gE Ab concentrations is >3.
- Evaluation of VRR for anti-gE humoral immune response at M2 after two doses of HZ/su in all subjects. The objective would be met if the LB of the 95% CI of the VRR for anti-gE humoral immune responses at M2 after 2 doses of HZ/su in all subjects receiving the vaccine was ≥ 60%.

There were additional secondary immunogenicity and safety objectives which included evaluations at additional timepoints during the study.

Reviewer comment: *There were no pre-specified immunogenicity objectives planned for evaluation of the OnChemo group only.*

The primary study endpoints were:

- Anti-gE humoral immunogenicity – anti-gE concentrations as determined by ELISA at M2
- Occurrence of AEs
  - Occurrence, intensity and duration of local solicited AEs and occurrence, intensity, duration and relationship to vaccination of general solicited AEs within 7 days after each vaccination
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during the 30 days after each vaccination according to MedDRA classification
  - Occurrence and relationship to vaccination of all SAEs and occurrence of pIMDs from first vaccination up to 30 days after last vaccination

Secondary endpoints included immunogenicity and safety assessments at additional timepoints.

Reviewer comment: *The Applicant chose not to evaluate the efficacy of HZ in this population.*

<u>Analysis populations</u>
The primary population for the analyses of safety were performed on the total vaccinated cohort (TVC), which consisted of all vaccinated subjects (subjects with at least one vaccination) according to the vaccine received. The primary populations for the analyses of immunogenicity were performed on the according to protocol (ATP) cohorts for immunogenicity; these were subjects who met eligibility criteria, who complied with the procedures and intervals as defined in the protocol, and from whom data concerning immunogenicity endpoints were available.

Study dates

Study initiation date: March 6, 2013
Study completion date: May 20, 2016

Demographics

The demographic composition of the TVC is presented below.

Table 70. Summary of demographic characteristics, Zoster-028 (TVC)

Characteristic	HZ/su N=117 n (%)	Placebo N=115 n (%)	Total N=232 n (%)
Age (years) at vaccination			
Mean (SD)	57.1 (10.8)	58.5 (11.7)	57.8 (11.3)
Median (min, max)	57.0 (35.0, 85.0)	59.0 (31.0, 87.0)	58.0 (31.0, 87.0)
Missing	0 (-)	0 (-)	0 (-)
Gender			
Female	70 (59.8)	69 (60.0)	139 (59.9)
Male	47 (40.2)	46 (0.0)	93 (40.1)
Ethnicity			
American Hispanic or Latino	5 (4.6)	6 (5.6)	11 (5.1)
Not American Hispanic or Latino	103 (95.4)	101 (94.4)	204 (94.9)
Geographic ancestry			
African Heritage/African American	2 (1.9)	2 (1.9)	4 (1.9)
American Indian or Alaskan native	2 (1.9)	0 (0.0)	2 (0.9)
Asian, East Asian heritage	11 (10.2)	14 (13.1)	25 (11.6)
Asian, South East Asian heritage	0 (0.0)	2 (1.9)	2 (0.9)
White, Arabic/North African heritage	1 (0.9)	0 (0.0)	1 (0.5)
White, Caucasian/European heritage	92 (85.2)	88 (82.2)	180 (83.7)
Other	0 (0.0)	1 (0.9)	1 (0.5)
Solid tumor diagnosis			
Bladder	1 (0.9)	4 (3.5)	5 (2.2)
Breast	53 (45.3)	52 (45.2)	105 (45.3)
Colorectal	25 (21.4)	22 (19.1)	47 (20.3)
Lung	8 (6.8)	13 (11.3)	21 (9.1)
Melanoma	1 (0.9)	0 (0.0)	1 (0.4)
Pancreas	1 (0.9)	1 (0.9)	2 (0.9)
Prostate	5 (4.3)	4 (3.5)	9 (3.9)
Other[1]	23 (19.7)	19 (16.5)	42 (18.1)
Performance status (ECOG)			
Fully active[2]	95 (83.3)	86 (74.8)	181 (79.0)
Restricted in physically strenuous activity[3]	18 (15.8)	28(24.3)	46 (20.1)
Ambulatory and capable of all selfcare[4]	1 (0.9)	1 (0.9)	2 (0.9)
Missing	3 (-)	0 (-)	3 (-)

Source: 125614/398.0 Zoster-028 CSR, Table 24, p. 155.
TVC = total vaccinated cohort, N = total number of subjects; n/% = number / percentage of subjects in a given category; SD = standard deviation
[1] Other includes gastric, endometrial, ovarian, head and neck, larynx, mouth sinus, tonsil, liposarcoma myxoid, liver, esophageal, renal, sarcoma, stomach, testicular embryonic carcinoma, thyroid, tongue, cervical, urothelial, uterine leiomyosarcoma
ECOG = Eastern Cooperative Oncology Group
[2] Fully active, able to carry on all pre-disease performance without restriction
[3] Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
[4] Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

The majority of subjects in the TVC were Caucasian and not of Hispanic or Latino ethnicity. The mean and median ages overall were 57.8 and 58.0 years respectively. The minimum and maximum ages in the treatment groups were 35 and 31 years and 85 and 87 years in the HZ/su and placebo groups, respectively. There were more females than males participating; subjects with breast cancer comprised 45.3% of the TVC. Of subjects in the TVC, none were <30 YOA and 61 (26%) were ≥30 and <50 YOA.

Although not presented here, the demographic composition of the ATP cohort for humoral Immunogenicity was similar to that of the TVC.

Reviewer comment: *The demographic composition of the TVC was similar between vaccination groups.*

Disposition and exposure

Of the 232 subjects in the TVC, 209 (90.1%) completed Visit 3. Of the 23 subjects withdrawn up to Visit 3, 15 subjects were in the HZ/su group and 8 were in the placebo group and consent withdrawal not due to an AE was the most common reason provided for withdrawal (for 11 and 5 subjects in the HZ/su and placebo groups, respectively. Of the 232 subjects in the TVC,180 (77.6%) completed the study. Of the 52 withdrawn up to completion, 27 were in the HZ/su group and 25 were in the placebo group. The most common reason for withdrawal up to study end was withdrawal due to an SAE (13 and 12 subjects in the HZ/su and placebo groups respectively - 12 and 11 in the HZ/su and placebo groups, respectively, were withdrawn due to fatalities).

The majority (90.5%) of subjects in the TVC received both vaccinations; 22 (9.5%) subjects did not receive a second vaccination [17 (14.5%) in the HZ/su group and 5 (4.3%) in the placebo group]. Of these subjects who did not receive a second vaccination, 12 out of the 17 in the HZ/su group and 4 out of 5 in the placebo group withdrew consent. The following subjects were withdrawn from vaccination (but not the study) at the investigator's discretion due to an AE:

- A 49 YO woman with breast cancer in the HZ/su PreChemo group reported the non-serious event of mild tachycardia judged related to vaccination by the investigator and did not receive dose 2. The Applicant provided information about this subject in an IR; tachycardia was reported immediately after the first dose of HZ/su which resolved the same day without treatment. The subject also reported a swollen tongue, of mild severity, on the day of first vaccination, which resolved without treatment on the same day and was also judged vaccine-related by the investigator.
- A 63 YO woman with lung cancer in the HZ/su PreChemo group reported the non-serious event of suspected HZ and did not receive dose 2.

Overall, 79.7% of subjects in the TVC (185/232) were included in the ATP cohort for humoral immunogenicity. From the HZ/su group, 74.4% (87/117) of subjects in the TVC were included and from the placebo group 85.2% (98/115) of subjects in the TVC were included. The most common reasons for exclusion from this cohort was essential serological data missing followed by subjects who did not complete the vaccination course.

Reviewer comment: *Due to subject characteristics (i.e., on or imminently anticipating chemotherapy), it is not unexpected that there would be reduced completion of the vaccination series and less than full participation in ATP immunogenicity cohorts.*

Safety results – solicited AEs

Solicited local (IS pain, redness and swelling) and general (fever, headache, fatigue, GI symptoms, myalgia and shivering)] events were recorded on a diary card for 7 days after each vaccination. Over 95% of TVC subjects in both treatment groups returned symptom sheets after each vaccination. The proportion of subjects in the TVC reporting at least one any grade or Grade 3 solicited AE (overall/subject) with both doses considered during the 7-day solicited AE reporting period is below.

Table 71. Percentage of subjects reporting at least one solicited AE overall/subject by treatment group in the 7-day reporting period, Zoster-028 (TVC)

	HZ/su	Placebo
≥1 solicited AE	95.5%	66.4%
≥1 Grade 3 solicited AE	25.0%	15.5%
≥1 solicited local AE	83.9%	6.4%
≥1 Grade 3 solicited local AE	11.6%	0.0%
≥1 solicited general AE	81.3%	66.4%
≥1 Grade 3 solicited general AE	22.3%	15.5%

Source: Adapted from 125614/398.0, Zoster-028 CSR, Tables 35 and 36, pp. 179
AE = adverse event; TVC = Total vaccinated cohort

Overall per subject, the most commonly reported solicited local event in the HZ/su group was pain. With both doses considered, overall per subject, 80.4% of subjects in the HZ/su group reported any grade pain as compared to 6.4% of subjects in the placebo group; of the HZ/su subjects, 9.8% reported Grade 3 pain (no subjects in the placebo group reported Grade 3 pain). With both doses considered, swelling (Grade 3) and redness (Grade 3) were both reported by 35.7% (1.8%) and 16.1% (0.0%) of subjects in the HZ/su group. The median duration of any grade of local symptoms in the HZ/su group (depending on the symptom) was 2 – 4 days.

The proportions of subjects in the TVCs of both treatment groups reporting any grade and Grade 3 specific solicited general events during the 7-day reporting period with both doses considered is presented below.

Table 72. Percentage of subjects reporting specific solicited AEs (any grade and Grade 3) overall/subject by treatment group in the 7-day reporting period, Zoster-028 (TVC)

	HZ/su	Placebo
Any grade fatigue	69.6%	61.8%
Grade 3 fatigue	14.3%	7.3%
Any grade GI symptoms	45.5%	44.5%
Grade 3 GI symptoms	5.4%	6.4%
Any grade headache	38.4%	36.4%
Grade 3 headache	5.4%	2.7%
Any grade myalgia	53.6%	28.2%
Grade 3 myalgia	10.7%	3.6%
Any grade shivering	34.8%	22.7%
Grade 3 shivering	5.4%	2.7%

Adapted from 125614/398.0, Zoster-028 CSR, Table 38, p. 184
AE = adverse event; TVC = Total vaccinated cohort

Overall by subject considering both doses, body temperature ≥37.5°C was reported by 17.9% and 4.5% of HZ/su and placebo group subjects respectively during the 7-day reporting period. During that period with both doses considered, body temperature ≥39°C was not reported by subjects in either treatment group. There was a trend for higher proportions of subjects in the

HZ/su group reporting any grade GI and Grade 3 symptoms after dose 2 (42.3% and 5.2%) as compared to dose 1 (28.6% and 1.8%), but there were also increases in any grade GI symptoms from dose 1 to dose 2 in the placebo group. The median duration of general symptoms in the HZ/su group was from 1 to 4 days.

Reviewer comment: *There was a high background rate of subjects reporting systemic symptoms during the 7-day reporting period in this population due to concurrent therapies.*

Overall per subject (considering both doses), during the seven-day reporting period, the proportions of subjects reporting solicited local AEs was higher (93.5%) in the 18 – 49 YOA HZ/su group, as compared to the ≥50 YOA HZ/su group (80.2%). Overall per subject (considering both doses), the proportions of subjects reporting at least one solicited AE or at least one solicited general AE also trended higher for the younger HZ/su subjects. Overall per subject (considering both doses), at least one Grade 3 solicited AE was reported by a higher proportion of younger (35.5%) as compared to older (21.0%) HZ/su recipients. While the proportions of younger and older HZ/su recipients reporting at least one Grade 3 local AE during the 7-day reporting period was comparable (12.9% younger group, 11.1% older group), the proportions of HZ/su recipients reporting at least one Grade 3 general AE during that period was higher for the younger (32.3%) as compared to older (18.5%) age group.

Safety results – unsolicited AEs

Unsolicited AEs (including SAEs) were collected on a diary card and recorded during the 30-day post-vaccination periods; tabulations of events were provided by MedDRA SOC and PT. During this period, of subjects in the TVC, 85.5% of subjects in the HZ/su group and 89.6% of subjects in the placebo group reported the occurrence of at least one unsolicited AE of any grade. The SOC Gastrointestinal disorders had the highest proportion of subjects reporting at least one AE contained in the SOC during the 30-day post-vaccination period; 50.4% and 55.7% of subjects in the HZ/su and placebo groups, respectively, reported at least one AE in that SOC. The most commonly reported AEs in the both treatment groups during the reporting period by PT were nausea and asthenia, reported by 26.5% and 25.6%% of subjects, respectively in the HZ/su group; both AEs were reported by 24.3% of subjects in the placebo group during the 30-day post-vaccination period.

Grade 3 non-serious unsolicited AEs were reported by 6.8% (N=8) of subjects (who reported 12 events) in the HZ/su group and 7.8% (N=9) of subjects (who reported 10 events) in the placebo group during the 30-day post-vaccination reporting periods. One event by PT was reported by more than one subject in each group; neutropenia was reported by 3 subjects each in both groups during the reporting period. One Grade 3 non-serious event (gastroenteritis with onset 14 days post-dose 1) in the HZ/su group was judged causally related to vaccination by the investigator.

Overall, 31 subjects (26.5%) in the HZ/su group and 33 subjects (28.7%) in the placebo group reported at least one unsolicited symptom with a medically attended visit (MAAE) during the 30-day post-vaccination period. The most frequently reported MAAEs during this period by PT were febrile neutropenia (4 subjects in the HZ/su and 2 subjects in the placebo groups), asthenia and nausea (3 subjects each in the HZ/su group and no subjects in the placebo group) in the HZ/su group; and vomiting (1 subject in the HZ/su and 4 subjects in the placebo groups), constipation

(no subjects in the HZ/su and 3 subjects in the placebo groups), anemia and neutropenia (each reported by 2 subjects in the HZ/su and 3 subjects in the placebo groups)in the placebo group.

Safety results – SAEs

From first vaccination to 30 days post-last vaccination, 16 subjects (13.7%) in the HZ/su group and 14 subjects (12.2%) reported an SAE. None were judged by the investigator as causally related to study treatment. The SAEs by PT reported most commonly during the 30-day post-vaccination period were febrile neutropenia (reported by 4 subjects in the HZ/su and 2 subjects in the placebo groups) and sepsis (reported by 2 subjects in the HZ/su group and no subjects in the placebo group) in the HZ/su group; and febrile neutropenia (see above), anemia, and acute kidney injury (no subjects in the HZ/su group and 2 subjects each in the placebo group). From 30 days post-last vaccination to study end, 30 subjects (25.6%) and 31 subjects (27.0%) in the HZ/su and placebo groups, respectively, reported at least one SAE. During this period, there was >1 report for the following SAEs in the HZ/su group: anemia, neutropenia, pancytopenia, diabetic ketoacidosis, malnutrition, bladder cancer (2 subjects each) and febrile neutropenia (3 subjects). During this period, there was >1 report for the following SAEs in the placebo group: pneumonia, sepsis, pulmonary embolism (2 subjects each) and neutropenia (3 subjects). None were judged causally related to study product by the investigator.

Reviewer comment*: The SAEs were reviewed, and there were plausible alternative etiologies for most of the events, which appeared to be, in the majority of cases, related to the underlying disease or chemotherapy.*

Safety results - fatal events

From first vaccination up to 30 days post-last vaccination, one subject in each treatment group died; neither death was judged to be causally associated with study product.

- HZ/su group – A 64 YO female with cervical cancer in the PreChemo group died of sepsis 4 days after dose 2.
- Placebo group – A 78 YO male with bladder cancer in the PreChemo group developed a pleural effusion 21 days after the first dose of placebo and died 5 days later.

From 30 days post-last vaccination to study end, 11 and 10 subjects in the HZ/su and placebo group, respectively, died. The fatal SAEs in both treatment groups were related to the underlying disease or treatments related to the disease. None were considered by the investigator to be related to study product. One fatal SAE had too few details for a determination of causality. That fatal SAE, coded as ‘death,’ occurred in a 63 YO male with lung cancer in the HZ/su group who had sudden onset of dizziness and dyspnea 37 days after the second dose of HZ/su and died shortly thereafter.

Safety results – AESIs

No pIMDs were reported from first vaccination to 30 days after last vaccination. One pIMD was reported from 30 days post-last vaccination to study end, a serious pIMD of autoimmune thyroiditis reported in the placebo group.

Cases of HZ

Three cases of suspected HZ were recorded during the study, 2 in the placebo group and 1 in the HZ/su group. The suspected HZ case in the HZ/su group was reported by a subject in the PreChemo group 13 days after dose 1.

Immunogenicity results – primary objective

The primary immunogenicity objective, analyzed on the ATP cohort was met, as the LB of the 95% CI of the GMR (HZ/su PreChemo group over placebo PreChemo group) for anti-gE Ab concentration at M2 after second vaccination was 17.9 (the pre-specified criterion was >3). The adjusted GMR was 23.2 (95% CI: 17.9, 30.0).

Immunogenicity results – secondary objectives

The results of five secondary objectives are presented below.

a) The secondary objective related to VRR (humoral immunogenicity) was met as the LB of the 95% CI of the VRR for anti-gE Ab concentrations in the HZ/su PreChemo group at M2 after two vaccinations was 85% (the pre-specified criterion was ≥60%). The VRR was 93.8% (95% CI: 85.0%, 98.3%).

b) The secondary objective related to the GMR (CMI) was met as the LB of the 95% CI of the GMR (HZ/su PreChemo group over placebo PreChemo group for gE-specific CD4 T cell frequencies at M2 after 2 vaccinations was 3.8 (the pre-specified criterion was >1). The observed GMR was 13.7 (95% CI: 3.8, 49.4).

c) The secondary objective related to VRR (CMI) was not met as the LB of the 95% CI of the VRR for gE-specific CD4 T cell frequencies in the HZ/su PreChemo group at M2 after 2 vaccination was 33.5% (the criterion was ≥50%). The observed VRR was 57.9% (95% CI: 33.5% – 79.7%).

As this objective was not met, per protocol the last 2 stated objectives were analyzed descriptively:

d) The observed adjusted GMR for anti-gE humoral response at M2 after 2 vaccinations in all subjects was 14.4 (95% CI: 10.7, 19.5).

e) The VRR for anti-gE humoral immune response at M2 after 2 vaccination in the HZ/su group in all subjects was 86.2% (95% CI 77.1%, 92.7%).

Reviewer comment: *The implications of the failure to achieve objective c above with regard to vaccine-mediated protection against HZ in this population is not known.*

In a response to an information request, the Applicant provided analyses of the humoral immune response in the OnChemo group only (the CMI subcohort consisted of subjects only in the PreChemo cohorts). The study was not designed or powered to evaluate these analyses; the number of subjects contributing data in these analyses were small.

- The adjusted GMR (HZ/su OnChemo group over placebo OnChemo group) for anti-gE Ab at M2 in the ATP cohort for humoral immunogenicity (N HZ/su subjects = 22 and N placebo = 18 subjects) was 8.8 (95% CI: 4.3, 18.1).
- The VRR for anti-gE Ab by ELISA at M2 in the HZ/su OnChemo group only was 63.6% (95% CI: 40.7%, 82.8%).

Reviewer comment: *Point estimates were lower for humoral responses (VRR and GMR) for the OnChemo as compared to the PreChemo group.*

Conclusion: *Zoster-028 was a small, heterogenous study enrolling several sub-populations of subjects with solid organ tumors, which were further sub-grouped by time of vaccination relative to chemotherapy (i.e., pre-chemo or on-chemo). The study also excluded subjects not receiving traditional chemotherapy (e.g., receiving only radiation therapy or targeted cancer therapies). While the heterogeneity of the population limits the ability to comprehensively assess risk:benefit in each subpopulation, it would be impracticable to evaluate HZ/su in all of the subpopulations of subjects with solid organ tumors by underlying disease and therapy. Furthermore, no safety signals were observed, and immune responses were demonstrated post-vaccination. Therefore, Zoster-028 is generally supportive of the safety and immunogenicity of the HZ/su vaccine in subjects with solid tumors receiving, or about to receive chemotherapy, And combined with the evidence of VE, safety, and immunogenicity from Zoster-002 and Zoster-039, these data support effectiveness and a favorable risk:benefit assessment of the use of the vaccine in this population*.

9.2.3 Zoster-015: Evaluation of HZ/su in subjects HIV-positive subjects

Zoster-015 was an observer-blind, placebo controlled, multi-center study which evaluated the safety and immunogenicity of HZ/su as compared to placebo when administered IM as a three-dose series (at M0, M2 and M6) to HIV positive adult subjects ≥18 YOA. Determination of the efficacy of HZ/su was not a study objective. A primary safety endpoint included worsening of the HIV disease (as determined by significant change to anti-retroviral therapy, occurrence of pre-defined changes in HIV viral load and/or CD4 T cell counts and/or occurrence of an acquired immune deficiency syndrome-defining condition). The primary immunogenicity endpoints included evaluation of CMI and anti-gE Ab responses at M7. Study participation time per subject was approximately 18 months (12 months after last vaccination). A total of 123 subjects (74 in the HZ/su group and 49 in the placebo group) were enrolled, vaccinated and included in the TVC (e.g., received at least one dose of study product).

Reviewer comment: *HIV disease progression was not observed following administration of HZ/su. Please see the review of Zoster-015 in the original BLA.*

9.2.4 Zoster-001: Early phase evaluation of HZ/su in subjects post-autoHCT

Zoster-001 was an observer-blind, placebo controlled, multi-center study which evaluated the safety and immunogenicity of HZ/su in comparison to gE combined with ½ dose $AS01_B$ adjuvant ($AS01_E$) as compared to placebo when administered as 2 or 3 doses (at M0, M1 and M3 or M1 and M3) to autoHCT recipients ≥18 YOA. Study results were to inform whether to pursue development of the vaccine in autoHCT recipients and, if so, the optimal vaccine schedule based on immunogenicity and safety data. Safety was a primary study objective, but there were

no disease-specific safety endpoints; recurrence of the underlying malignancy for which the autoHCT was performed was recorded separately throughout the study. The primary immunogenicity endpoints included evaluation of CMI and anti-gE Ab responses at M4. Study participation time per subject was approximately 18 months (12 months after last vaccination). A total of 120 subjects (90 in the 3 active vaccination groups and 30 in the placebo group) were included in the TVC.

Reviewer comment: *Disease recurrence after administration of HZ/su or gE/AS01$_E$ as compared to placebo was not observed. Please see the review of Zoster-001 in the original BLA.*

10. CONCLUSIONS

As in the general older adult population (≥50 YOA) evaluated in the original BLA, in IC subjects 18 years of age and older, local and/or general solicited symptoms, generally of short duration, were reported in the majority of subjects evaluated in the HZ/su group. Severe reactogenicity was not uncommon and reported more frequently in the younger age stratum. Overall, deaths, SAEs and pIMDs were reported in similar proportions of subjects in the HZ/su and placebo groups. Routine pharmacovigilance will surveil for rare adverse events including pIMDs which may not have been observed given the sample size evaluated in the clinical studies. An observational comparative study is proposed to evaluate the safety of HZ/su in IC pregnant women.

HZ VE was demonstrated in Zoster-002 in adults who had received an autoHCT 50 – 70 days prior to vaccination. In Zoster-039, HZ cases were prospectively monitored and adjudicated in a similar manner as Zoster-002, in order to assess HZ incidence. In a post hoc analysis for Zoster-039, HZ VE was demonstrated in adults with hematologic malignancies undergoing or having recently completed immunosuppressive chemotherapy. Additional studies submitted to the sBLA provided assessments of safety and immunogenicity in adults with kidney transplants, solid organ tumors on chemotherapy, and HIV+ subjects. For the purposes of this sBLA, they also provided evidence of the overall safety and humoral and cellular immunogenicity of HZ/su in several IC conditions, supporting the effectiveness and a favorable risk:benefit profile in a broad population of IC individuals.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 73. Risk-Benefit Considerations of Vaccination with HZ/su in IC Adults ≥18 Years of Age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Most individuals in the US are latently infected with VZV. • Acute HZ-associated pain can be severe and debilitating. • The complications of HZ are serious and include persistent neuropathic pain (i.e., PHN), viral dissemination, stroke, encephalitis, and visual impairment including blindness. • Immunosuppression or immunodeficiency are major risk factors for HZ and HZ-related complications. • Risk of HZ in the immunocompromised population varies by underlying condition and therapies	• Immunocompromised adults are at increased risk for HZ and HZ-related complications compared to the general population. • HZ is associated with substantial morbidity, which can be acute and/or chronic. • Based on the debilitating impact on physical and psychological well-being, HZ is considered a serious condition.
Unmet Medical Need	• HZ/su is currently licensed for use in persons 50 years of age and older. There is no vaccine licensed for prevention of HZ for use in individuals 18 – 49 years of age who are or will be at increased risk for HZ due to immunodeficiency or immunosuppression caused by disease or therapy. • Available preventive therapy includes long-term, off-label use of antiviral medications. • The treatment of HZ includes time-sensitive administration of antiviral medications and therapeutics for pain control, including opioids. • PHN, the most common HZ-associated complication, can be refractory to treatment.	• There is a need for a vaccine for the prevention of HZ licensed for use in immunocompromised individuals 18 – 49 years of age. • An effective preventive vaccine against HZ may obviate the need for time-sensitive antiviral medication and use of medications for adequate pain control.

Clinical Benefit	• HZ VE of 68.2% (95% CI: 55.6, 77.5%) was demonstrated in Zoster-002, a randomized, placebo-controlled, clinical endpoint efficacy trial, enrolling adults post-autoHCT. • HZ VE of 87.2% (95% CI: 44.2%, 98.6%) was demonstrated in a post hoc efficacy analysis in Zoster-039, a randomized, placebo-controlled trial, enrolling adults with hematopoietic malignancies who had recently completed or were undergoing chemotherapy. • HZ VE was comparable across the pre-specified age strata (18 – 49 YOA and ≥50 YOA) and genders. There were no statistically significant differences in VE by regions. Low enrollment precluded demonstration of HZ VE in some demographic subgroups. The study was not designed to evaluate efficacy based on demographic subgroups. • The effect of some specific immunosuppressive therapies, prophylactic antiviral therapy, and some underlying diseases on HZ VE is not known. • Other factors that may affect efficacy (e.g., timing of vaccination with respect to chemotherapy cycle) were not evaluated. • Immune responses were observed in most IC populations for which data was submitted (solid organ tumors undergoing cancer therapy, renal transplant, HIV+).	• The clinical benefit of HZ/su was demonstrated in a population with a high risk of HZ (post-autoHCT) and during the time of highest risk, as well as another high-risk IC population (individuals with hematologic malignancies). Evidence of clinical benefit was observed in autoHCT recipients18 – 49 YOA. • Clinical benefit in other IC populations is supported by the demonstration of efficacy in these two different IC populations, and this is supported by evidence of comparable immune responses in several other IC populations. • The clinical studies were conducted in individuals with a variety of underlying diseases and therapies. The effect of specific immunosuppressive treatments, antiviral therapies, and underlying diseases on HZ/su efficacy is unknown.

Risk	• Safety was not evaluated in all IC populations; collection of such data in all IC populations is likely impractical. • In some of the IC populations evaluated, sample size was too small to fully characterize the safety of the vaccine. • Some pertinent disease-specific safety events of interest were not systematically evaluated post-vaccination (for example, indicators of graft function and alloimmunity in the post-renal transplant population). • Reactogenicity was commonly reported. In Zoster-002, 85.8% and 75.2% of autoHCT subjects reported solicited local and general symptoms following HZ/su, respectively. • Severe reactogenicity was common. In Zoster-002, 13.2% and 14.2% of autoHCT subjects reported Grade 3 solicited local and general symptoms, respectively. • Solicited local and general symptoms were reported more frequently and at greater severity in 18 – 49 YOA compared to ≥50 YOA subjects. • Most solicited general symptoms were reported more frequently and tended to have greater severity after dose 2 as compared to dose 1. • Most reactogenicity events were mild or moderate and of short duration. • Imbalances (HZ/su > placebo) in the occurrence of some AEs were observed. In the integrated safety analysis, pneumonia, arthralgia, and influenza-like illness were observed in at least 1% of the HZ/su group and at 1.5 times or greater in the HZ/su group compared to the placebo group. • In general, the occurrence of unsolicited AEs, SAEs, pIMDs, deaths and the disease-specific safety outcomes that were evaluated were comparable between vaccination groups in all six studies submitted. SAEs of pneumonia were also reported more frequently in the HZ/su group (1.3%) compared to the placebo group (0.7%); causal association with vaccination was not established. • An increased risk of GBS has been identified in a post-marketing observational study. No GBS was observed in association with vaccination in the submitted studies, but the studies were not designed to assess GBS risk.	• The observed reactogenicity may increase health care utilization among IC HZ/su vaccinees, in whom the threshold for initiating clinical evaluations and therapeutic medications may be low. • The safety database submitted for subjects 18 – 49 YOA in Zoster-028, Zoster-041, and Zoster-015 was small, which limits the ability to fully characterize risk. • It is unknown if there are specific risks in certain IC populations that were not adequately evaluated. • Despite the limitations of the safety database, the overall safety profile, including post-marketing surveillance of both immunocompetent and IC adults ≥50 YOA, supports licensure of HZ/su in IC subjects.
Risk Management	• The proposed pharmacovigilance plan includes routine, enhanced, and active pharmacovigilance activities that are ongoing. • An observational comparative trial of safety in pregnant IC women is proposed.	• As proposed, the pharmacovigilance plan is adequate to manage the risk of HZ/su vaccination.

11.2 Risk-Benefit Summary and Assessment

HZ/su is U.S. licensed to prevent HZ in individuals 50 YOA and older regardless of any underlying medical conditions. Risk of HZ in immunocompromised individuals of any age is increased over the general population and HZ can cause significant and prolonged morbidity in this population. Therefore, an unmet medical need exists for immunocompromised individuals 18 – 49 YOA. In Zoster-002 efficacy was prospectively evaluated and was demonstrated in individuals who are at particularly high risk of HZ, those who had received an autoHCT. In Zoster-039, efficacy was demonstrated in a post hoc analysis in the IC population of individuals with hematologic malignancies. Safety was evaluated in a total of six trials in five IC populations, representing 1,587 IC subjects who received at least one dose of HZ/su. Local and systemic reactogenicity with HZ/su are common. Overall, SAEs, deaths, and pIMDs were reported in similar proportions of subjects in HZ/su and placebo groups during select time periods evaluated. An imbalance in SAEs of infective pneumonia was observed up to 30-days post-last vaccination (1.3% and 0.7% in the HZ/su and placebo group, respectively); a causal association with vaccination was not established. Unsolicited AEs reported more frequently in the HZ/su group compared to the placebo group in the 30 days post-vaccination were pneumonia (1.5% and 0.9%, respectively), arthralgia (1.5% and 1.0%, respectively), and ILI (1.3% and 0.6%, respectively). Although GBS was not reported in association with vaccination in this submission, in postmarketing data GBS was associated with HZ/su vaccination.

There are many IC populations, and there is heterogeneity within each population; as such it would be impracticable to evaluate HZ/su in each IC population or sub-population, or at the many potential timepoints relative to administration of immunosuppressive therapies. However, the demonstration of efficacy in two different IC populations, including one population at high risk of HZ at a time of greatest risk (autoHCT), and demonstration of a comparable immune response in three other populations (solid organ tumor, renal transplant, HIV-positive), provide substantial evidence of effectiveness of vaccination in a broad population of IC adults. The acceptable safety profile further supports a favorable risk benefit profile in IC populations at increased risk of HZ.

11.3 Discussion of Regulatory Options

The Applicant has requested, and the data from the six studies submitted in this sBLA support, “traditional” approval extending the population for use of HZ/su to include individuals 18 through 49 years of age who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression. The Applicant proposed language for the Indications and Usage section of the PI to add “use in adults 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy” (in addition to previously approved use in adults 50 years of age and older). Use in individuals anticipating an increased risk of HZ due to planned immunosuppression is supported by data from Zoster-028, in which a subgroup of subjects received their first vaccination prior to the start of chemotherapy. The Applicant also proposed modification of the dosing regimen to allow for dosing at a one to two month interval for immunocompromised individuals who would benefit from a shorter vaccination schedule, which is supported by the studies submitted, each of which used a 1 to 2 month interval between doses 1 and 2.

11.4 Recommendations on Regulatory Actions

The clinical reviewers recommend approval, extending the use of HZ/su in IC adults 18 through 49 years of age who are or will be at increased risk of HZ due to immunodeficiency or

immunosuppression caused by known disease or therapy, the new dosing regimen for IC adults 18 years of age and older, and the associated revisions to the Indications and Usage section and the Dosing and Administration section of the PI, as above.

11.5 Labeling Review and Recommendations

CBER requested several changes to the proposed PI, including the following: presentation of the solicited AEs (to include dose 1 and dose 2 and to be based upon Zoster-002 instead of the integrated safety data), addition of two unsolicited AEs reported more frequently in the HZ/su group compared to the placebo group (pneumonia and ILI), addition of reported frequency of pneumonia SAEs, removal of select secondary and tertiary efficacy endpoints, and presentation of the safety and efficacy information to clarify elements of the study design (number of subjects, safety follow-up, pre-specified or post hoc efficacy analysis).

11.6 Recommendations on Postmarketing Actions

The Applicant proposed an observational postmarketing commitment (PMC) study to monitor and to evaluate pregnancy exposures to HZ/su (Shingrix) and outcomes in women who are between 18 and 50 years of age (YOA) and immunodeficient or immunocompromised due to disease or therapy. Routine enhanced and active pharmacovigilance will continue similar to ongoing activities since the time of the original approval.

Reviewer comment: *CBER concurs with the post-marketing commitment as proposed by the Applicant. Please refer to section 4.6, section 9.1.1 and the pharmacovigilance review for further details regarding post-marketing activities and pharmacovigilance.*